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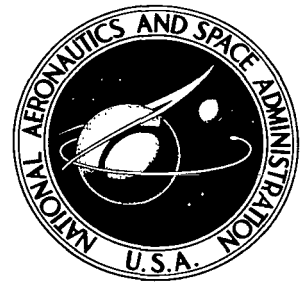

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THE NERVOUS SYSTEM AND "STRESS"

(The Principle of Dominance in Pathology)

by G. I. Kositskiy and V. M. Smirnov

"Nauka" Press, Moscow, 1970

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THE NERVOUS SYSTEM AND "STRESS"

(The Principle of Dominance in Pathology)

By G. I. Kositskiy and V. M. Smirnov

Translation of: "Nervnaya Sistema i 'Stress'"
(O Printsipe Dominanty v Patologii).
"Nauka" Press, Moscow, 1970

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ANNOTATION

The book presents the results of experimental investigations indicating that the action of supplementary nonspecific stimuli on the organism produces a significant increase in the resistance of the organism to pathogenic stimuli, which is of great importance in the prophylaxis of disease. A critical role in the development of these phenomena is assigned to the phenomena of the inhibition of pathological processes by the creation of a "nonspecific focus" of the dominant stimulus.

"Why is the pathological state not our affair? On the contrary, it is precisely the physiologist with his ability to take methodical and logical approaches to the study of life who is the rightful worker in this field."

I. P. Pavlov

(Collected Works, Vol. II. Moscow - Leningrad, 1946, p. 348).

FOREWORD

The present book is concerned with the mechanisms of the change of reactivity of the organism under the influence of so-called nonspecific stimuli. In his experimental investigations, beginning in 1953, the author of this foreword was able to show that such actions as injection of turpentine, production of artificial pneumothorax, action of faradic current on the sciatic nerve, etc., can produce a sharp rise in the resistance of an organism and inhibit many pathological processes.

The development of these pathological processes involves the participation of the nervous system to a greater or lesser degree, and we could therefore assume that supplementary nonspecific stimuli act primarily on the neuro-reflex components of pathological reactions, thereby altering the course of the process as a whole. By that time, however, we had become acquainted with the work of H. Selye, who treats similar phenomena from a different point of view.

Selye introduced the term "chiasmic resistance" to designate similar phenomena, assuming that the change in the reactivity of the organism under the influence of nonspecific stimuli depends on the production of so-called "adaptive hormones." The teachings of Selye regarding "stress" have been widespread, as we know. Selye and his associates have published over 1700

papers on this subject. Thirty-nine monographs by Selye devoted to "stress" have appeared in different languages. In our troubled times, with so much going on and with man in the grip of ever-increasing stress, the word "stress" has become a sort of symbol of the times and their effect on the organism. The number of publications on stress in all nations totals tens of thousands, and it is impossible for an investigator to review them. The concept of Selye and his followers has in fact ignored the role of the nervous system in pathology and the principles of nervism in general. Moreover, the nervous system plays an important and leading role in all the reactions of the organism, both physiological and pathological.

Since our treatment of the phenomena of the increase in resistance of the /4 organism under the influence of supplementary nonspecific stimuli proceeded from a recognition of the primary role of the nervous system in these phenomena, and, consequently, differed in theory from Selye's treatment, it was necessary to conduct studies which would make it possible to answer the question of which viewpoint is more correct. Since 1961, V. M. Smirnov (who was then a student and is now a member of the scientific group at the Department of Physiology) has participated in our experimental work. During the last ten years, we have twice undertaken an experimental proof of several aspects of Selye's concept. These tests failed to support a number of the basic concepts of the latter school and showed that the mechanisms of nonspecific resistance cannot be attributed to changes in the level of "adaptive hormones" in the blood, but are much more complex in nature. It is the nervous system which plays the principal and crucial role in the regulation of the phenomena of reactivity of the organism.

In this book, we are presenting the results of these experimental investigations for the reader to evaluate. It is possible that this book will serve, not only as a summation of this stage of the experimental polemic with Selye, but also as an attempt at further development of the principle of nervism which (we are deeply convinced) was and still is the cornerstone of medical theory.

Chapters I, V and a large part of II were written by G. I. Kositskiy, while Chapters III, IV and part of II were written jointly by both authors. We should like to express our gratitude to A. A. Markova for the editorial comments she made in reading the manuscript.

Prof. G. I. Kositskiy

Head of the Department of Physiology,
Second Moscow Medical Institute imeni N. I. Pirogov

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CHAPTER I.

THE NERVOUS SYSTEM AND PATHOLOGICAL PROCESSES

Even the doctors of antiquity were well acquainted with the significance of psychic and moral factors in preventing illness. /5*

"The straining of the mind toward some goal brings courage with it, always directed to the strengthening of life," wrote Hippocrates. "Happy people always get better," declared Ambrose Paré, while Seidenheim said that "the arrival of a clown in town is better for the health of the inhabitants than dozens of mules loaded down with medicines." The great Russian surgeon, N. I. Pirogov, showed remarkable insight when he remarked that the wounds of soldiers in a retreating army heal more slowly than those of the victors.

The famous Russian physician, S. P. Botkin, felt that the nervous system was extremely important in both the development and prevention of disease. Botkin, together with I. M. Sechenov, was largely responsible for laying the foundations of the scientific school which has been called "nervism", characterized by an effort to extend the influence of the nervous system to the largest possible number of processes in the organism.

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*Numbers in the margin indicate pagination in the original foreign text.

Nervism in Pathology

The physiology of the intact organism, founded by I. P. Pavlov, was the basis of a new stage in the development of nervism. The objective study of the behavior of an organism and the founding of the physiology of higher nervous activity made it possible to study the important role of signals from the outside environment and conditioned reflex mechanisms in the development of pathological processes. I. P. Pavlov showed that "extreme stimuli" of the nervous system can cause serious damage in many organs and systems which can be termed pathological reflexes.

All of these studies were continued and expanded by the co-workers and pupils of I. P. Pavlov.

A. D. Speranskiy studied the causes and mechanisms of the development of so-called "nervous dystrophies", revealed the reflex mechanism of the development of many illnesses and pathological disorders, and showed how to cure them by working on the nervous system. /6

A significant contribution to the development of nervism was made by M. K. Petrova. In her experiments, she studied the effects of overstraining the stimulatory and inhibitory processes in the human cerebral cortex and disruption of higher nervous activity on the organism of experimental animals. One group of animals was used in a systematic study of conditioned

reflexes, in which a certain schedule of work and rest was maintained, and the nervous systems of the animals were protected against overstrain and extremely difficult problems. Another group of animals was subjected to tests that produced systematic overstrain of the nervous processes in the brain cortex. The latter group of dogs was faced with difficult problems which caused overstrain of the nervous system, so that experimental neuroses developed. After several years of conducting these tests, a result was obtained which even the experimenter himself did not anticipate.

All the dogs which had been subjected to nervous traumas developed various pathological conditions. The animals lost weight rapidly, shed their fur, and developed eczema, furuncles and ulcers, which they did not long survive. Muscular weakness did not allow these animals to mount the stand for their tests, even if a step-stool were placed next to it. The dogs aged and became decrepit rapidly. Malignant tumors developed in several instances. All of these pathological processes developed without the specific action of poisons, germs, etc., but merely by changing the signals from the environment, the effect of various conditional stimuli and various problems that placed a strain on the nervous system, which could be termed a disruption of the normal equilibrium of nervous processes in the brain cortex and lead to neurosis.

"However, those animals that had been shielded from nervous traumas, whose nervous systems were given optimum conditions for normal function, remained in complete nervous equilibrium all the time ... In contrast to the neurotraumatized animals, as we have already said, they were completely free of any cutaneous and neoplastic processes of the internal organs," writes M. K. Petrova. "All of them, though older than the neurotics (by 1 to 3 years), still looked much younger; their muscle tone was high, they scrambled rapidly up the stairs to the laboratory and bounded onto the stand. They all lacked any signs of a rapidly aging organism, as were seen in the neurotics." (Petrova, 1946). These dogs lived much longer than the neurotic ones.

"Thus, we were taken completely by surprise by the fact of the important problem of aging, and especially by the cause of premature aging of the organism," writes M. K. Petrova. "Our experimental data indicate that the /7 central nervous system plays the initial and principal role in the process of aging of the organism, mainly the cerebral cortex and the other systems linked with it" (Petrova, 1946).

Another pupil of Pavlov, Academician K. M. Bykov, found a close relationship between the cerebral cortex and the functions of the internal organs. He showed that the activity of the internal organs, like the behavior of animals, can be regulated by the cerebral cortex through the mechanism of conditioned reflexes. Bykov and his associates observed that extremely interoceptive stimuli can lead to the development of isolated areas of increased excitability in the cerebral cortex and the adjacent subcortex. The circulation of afferent and efferent impulses between such an area and some internal organ forms a unique "vicious circle" that continually maintains pathological reflexes which lead to persistent disturbances of the functions of that organ. In this manner, the cortico-visceral theory of pathogenesis was formulated for several ailments.

A. O. Dolin showed that the development of many pathological processes (sometimes even fatal ones) is possible, depending on the type of conditioned reflexes. Thus, disturbances that are initially functional can turn into persistent organic injuries.

The participation of the nervous system in the development of pathological processes is not limited to the latter alone. Any disease, as we know, is a disturbance of the vital activity of an organism, developing under the influence of excessive stimuli from the external and internal environments. This results, on the one hand, in the appearance of the phenomenon of "breakdown", i.e., damage to some functions and structures of the organism, and on the other hand, to processes of protection, i.e., the taking of "physiological measures" against the harmful agent, as well as compensatory processes. At various stages of development of any disease, these three types of reaction

(damage, protection and compensation) may be manifested to varying degrees. These reactions are sometimes so closely interwoven in a single syndrome that it is simply impossible to separate them. At certain stages of illness, such strong phenomena of "protection" and "compensation" arise that they themselves begin to constitute a definite danger to the organism. Serious harm to the organism and even death sometimes occur not because of the damage done by a disease-producing agent, but because of the extremely pronounced "protective" reactions of the organism. All protective reactions, like all processes of the vital activity of the organism in general, are subject to the regulatory action of the nervous system. Hence, the debate over what the /8 nervous system actually "organizes", the "disease" or the "physiological measures" against the disease, is pointless in itself. Disease is often the result of an extremely severe "physiological measure".

The nervous system regulates all the functions and forms all the reactions of the organism, and it is natural that it retains this role even when "extreme stimuli" are acting on the organism. Protective reactions are primarily the reactions of specialized systems of the organism whose functional intensity is regulated by the nervous system. The compensation processes, on the one hand, are the result of the development of new systems of conditioned reflexes which "fill the gap" in the system of reactions of the organism that develops as the result of "breakdown" and death of certain structures (Asratyan, 1953); on the other hand, compensation processes develop with an increase in the functional intensity of the intact structures, organs and tissues to ensure performance of a specific function.

The role of the nervous system in the development of protective reactions, i.e., "physiological measures against disease" is obvious and does not call for any special remarks. We must dwell in somewhat more detail on the question of the participation of the nervous system in certain "breakdown" reactions, i.e., damage to the organism under the influence of "extreme stimuli". We know that in the course of evolution the nervous system has become specialized as a system that receives external and internal signals and then analyzes, stores and transmits the information. These properties of the

nervous system, of course, manifest themselves in cases when the organism is subject to "extreme stimuli". Although a pathogenic agent by its direct action may harm not only the nervous system, but any organ or tissue, its effect is often directed primarily at the afferent nerve apparatus in the tissues. Their excitability with respect to the action of adequate stimuli, of course, is much greater than the direct excitability of cells and tissues. But the "extreme stimuli" may be inadequate (i.e., there are no specialized receptors for them). The excitability of the afferent nerve apparatus with respect to these stimuli may be the same as the excitability of the surrounding tissues. Even in the latter case, however, the nervous system may participate in the reaction to a greater degree than the other tissue elements or may be insufficiently sensitive to the action of the pathogenic stimulant itself. On the other hand, it may react very delicately to changes in the organism and tissues that arise under the influence of the latter.

Hence, the involvement of the nervous system in a reaction under the influence of a pathogenic stimulus is linked either to a direct or indirect reception of the stimulus. However, the subsequent reactions and changes in the organism depend in large measure on the effect of the stimulus on the /9
nervous system. Denervation of the organ or tissue, as well as total inhibition of the nervous system (under anesthetic) can of course alter the course of a number of pathogenic processes. Some pathological reactions can themselves take the form of conditioned reflexes (A. O. Dolin). In man, a signal of this kind may be a word which in certain cases can harm, cause serious damage and even kill (Platonov, 1962).

We have said enough to be able to characterize in a very general form the role of the nervous system in the development and growth of pathological processes. We know, however, that the nervous system participates in the regulation of the processes of vital activity of organs and tissues (in the normal and pathological states) in a "union" with the humoral regulation mechanisms, especially with the endocrine glands. Although the endocrine glands and other humoral regulatory factors are merely individual links in the composition of nervous regulatory effects, it is necessary to consider

the processes of nervous regulation without these links. In exactly the same way, it is completely useless to attempt to absolutize these links and the assumption that they alone can produce the adaptation reaction.

An immense body of literature is devoted to the role of the nervous system in pathology. Lacking space here to discuss these important problems, we refer the reader to a number of monographs, papers and collections of articles devoted to the problem of nervism in pathology (Ado, 1953; Asratyan, 1953; Borodulin, 1949; Bykov and Kurtsin, 1960; Galkin, 1944; Dolin, 1952; Speranskiy, 1935, et al.)

We will dwell only briefly on the question of the role of the nervous system in the development of "typical" pathological processes: disorders of the blood circulation, thromboses and emboli, atrophies, dys- and hypertrophies, metabolic disturbances, vascular permeability, processes of regeneration and the growth of tumors, since our own experimental studies are concerned with these matters.

Disturbances of the blood circulation. The principal regulator of the blood circulation, as we know, is the demand of the tissues for oxygen and nutrient substances. All of the different adaptive reactions of the hemodynamic apparatus for various states of the organism are achieved primarily through neuroregulatory mechanisms.

Naturally, pathological changes in hemodynamics, accompanied by a change in the adaptive reactions, do not constitute an exception. These disturbances arise either as the result of damage to the nervous regulatory mechanisms or (in individual cases) are manifestations of compensatory and protective reflex reactions by the organism which occur with the participation of the nervous system but are extremely pronounced.

Thromboses and emboli. The question of the role of the nervous system /10
in the regulation of blood coagulation processes and the functioning of the anticoagulant system has been the subject of a large number of studies, which

were surveyed by A. A. Markosyan (1960), B. A. Kudryashchov (1960) and other authors. In many cases, the development of thromboses is connected with a disruption of these normal regulating effects. The problem of the role of the nervous system in the development of reactions to an embolus will be discussed in detail later on (in describing our own experiments with emboli).

Trophic disorders. We know that "function shapes the organ." In fact, it is activity which supports the very structure of the living tissue; an increase in the intensity of function of any organ or tissue will lead to hypertrophy, specifically to an increase in the mass of the functional protein structures.

The relationship between the intensity of the organ functions and the rate of protein synthesis makes it possible to understand the mechanisms of the trophic function of the nervous system and the reasons for the development of so-called "nervous dystrophy."

The intensity of the processes of vital activity of an organism and its individual structures is governed by the regulatory activities of the nervous system. A change or disruption of the function of the nervous regulatory apparatus obviously can have an effect on the processes of the "plastic guarantee of functions" and lead to the appearance of trophic disorders. Of course, the problem of the role of the nervous system in the development of dystrophic processes has itself been the subject of many years' careful study and has been discussed in a great many specialized works (Pavlov, 1920; A. Speranskiy, 1935; A. V. and A. A. Vishnevskiy, 1952, etc.).

Involvement of the nervous system in the development of inflammatory processes. The development of all components of an inflammatory reaction, which include vasodilatation (hyperemia), increased permeability of vascular walls, appearance of edema, alteration of tissues, as well as cell reactions is the object of regulatory actions of the nervous system. We are reminded of the role of the nervous system in circulatory disturbances and phenomena of alteration and dystrophy. Likewise, other components of the inflammatory

process, such as permeability of the vascular wall and cell reactions, are dependent on the regulatory phenomena of the nervous system.

The well-known works of K. M. Bykov (1944) and his co-workers showed that it was possible to have changes in permeability produced by conditioned reflexes. In these experiments, a combination of a previously indifferent stimulus (conditioning signal) with some unconditioned effect that changes the state of permeability meant that the most indifferent stimulus became an active agent and actively changed the process under study.

We should also mention the large number of observations which indicate a change in vascular permeability in man under the influence of verbal sugges- /11
tion in a hypnotic trance (Platonov, 1962). A typical second-degree burn — development of tissue alteration and considerable exudate — was observed following simple verbal suggestion that "a hot object is being applied to the skin."

The question of the change in permeability of vascular walls and changes in the hemato-parenchymatose (histohematic) barrier will be discussed in more detail in the next chapter in describing adrenalin edema of the lungs.

Processes of tissue regeneration and tumor development. I. V. Davydovskiy (1961) emphasizes the important role of the nervous system in regeneration processes. He presents a number of facts which indicate that disruption of the innervation of organs and tissues inhibits regeneration processes. As we know, the matter of regeneration is linked not only with the restoration of a mass of material substrate but also with the very rapid stimulation of this substrate to activity, since the "very fact of inclusion completes the regeneration process and confers on it the outlines of biological and functional completeness." However, the actual stimulation to function and the regulation of the function of organs and tissues is accomplished, as a rule, by the nervous system.

There are many observations which show that the nervous system plays a part in the development and growth of many tumors. Clinicists are familiar with the significance of psychic traumas, overstresses and disruptions of higher nervous activity as factors which favor the appearance of malignant tumors. These data agree with the works of M. K. Petrova cited above.

We should keep in mind the large number of experimental data on the fact that the transplantation of tumors or their induction by cancerogenic substances is accomplished more readily in cases where local tissue innervation has been disrupted. Detailed abstracts of these experiments are to be found in the works of N. N. Petrov (1947) and I. M. Neyman (1961).

Hence, the nervous system is involved in the development of fundamental, "typical" pathological processes. But since the syndrome of any disease usually consists of different combinations of these "typical" processes, it is clear that the nervous system plays a very important part in the development of the individual elements of the syndrome of any disease.

This makes it understandable why certain effects on the nervous system can aid in the prevention and cure of many ailments. We have in mind the change in the nature of the development of many pathological processes in the anesthetized state (Galkin, 1944) or in hibernation (Kalbukhov, 1946), the curing by sleep of not only neuro-psychic, but certain somatic ailments (Asratyan, 1953), treatment with novocaine block (A. V. and V. V. Vishnevskiy, /12 1952), therapy using the action of a supplementary nonspecific stimulus (Speranskiy, 1946) and many other methods of influencing the pathological process through the nervous system.

It is not the purpose of this book to deal with these questions. We must examine the significance of only one of the important principles of the functioning of the nervous system, to wit: the principle of dominance in the development (and especially the prevention) of certain pathological

processes. To do this, we must begin by examining in greater detail the basic outlines of the theory of A. A. Ukhtomskiy regarding dominance.

A. A. Ukhtomskiy's Theory of Dominance

As we know, the concept of dominance began to take shape under the influence of facts obtained in experiments involving stimulation of the cerebral cortex.

"In the spring of 1904," recalls A. A. Ukhtomskiy, "I chanced to make the following observation: while preparing a dog for one of N. Ye. Vvedenskiy's experiments on the motor region of the cerebral cortex, I was determining the location and excitability of the cortical centers of the forelegs, using faradic currents and applying them with the usual bipolar transferable (platinum) electrodes. This took place approximately 30 minutes after bilateral exposure of the cortex and at a time when the chloroform anesthetic used in the operation had not been administered for 20 minutes. I was soon struck by the following phenomenon: following a series of more or less pronounced movements which I succeeded in producing in the forelegs from the cortex, the excitability of the corresponding cortical areas innervating these movements of the extremities decreased suddenly; applying the electrodes to the points from which I had just evoked very clear and definite movements in the shoulders and upper forelegs, in the prepared digital extensor, I was now not obtaining any kind of definite movement, but instead was beginning to evoke weak movements in the tail. Somewhat confused, I began to increase the stimulating current, then applied the electrodes once again to the same points on the cortex which usually innervate the forelegs; now, with increased stimulation, the following picture became very clear: no movements were visible in the forepaws, but instead each stimulus of the cortex resulted in the tail being raised, the amount of lift increasing with the current intensity. Then suddenly the contents of the large intestine were expelled, evidently with great force; almost immediately afterward, the centers for the forelegs began to act normally, i.e., when currents were applied to the corresponding points in the cortex,

the previous definite movements of the forepaws began to show up once again. The thresholds of cortical excitability of the forelegs even decreased somewhat for a period of time relative to what they were prior to the above-described temporary "decrease in cortical excitability."

At that time, back in 1904, I did not see any clear physiological meaning in this observation, but the combination of phenomena per se interested me, and I wrote it down so as not to forget. Later on, as I became gradually more acquainted with inhibition processes in the nervous system, under the guidance of Prof. N. Ye. Vvedenskiy, I began to surmise that in this observation, in all probability, I had been dealing with the phenomenon of chronological inhibition of cortical innervation of the forelegs. From this viewpoint, however, the relationship between the phenomena in the observation described above is of interest for still another reason: stimulation of the cortical centers for the extremities did not evoke movement in the latter, but failed to reach them and each time evoked a movement of the tail until, finally, the act of evacuating the bowels occurred. A stimulus that arose in the cortical centers for the forelegs, instead of going to the latter in the usual fashion, so to speak, took other, unconventional pathways that innervate the tail and in all probability the intestine as well. From the standpoint of the theory of inhibition and corroboration of the stimuli, the phenomenon can be interpreted as follows: the cortical innervation did not cause visible effects on its usual pathways because of inhibitions that developed along them, and at the same time produced corroborations of stimuli on other, separate pathways." (Ukhtomskiy, 1911, pp. 31-32). /13

In 1911, a work appeared that was devoted to comprehensive experimental study of similar facts. It showed that the reactions of an animal when a specific motor region of the cortex is stimulated are not stereotyped. They depend on the functional state of the central nervous system as a whole, which is determined by the nature of the afferent impulses reaching the brain.

In the case when the test stimulus is preceded by the arrival in the cortex of powerful signals from other organs, the reaction of the organism changes. Thus, for example, previous distension of the large intestine means that the test stimulus does not produce the usual withdrawal of the paw, but the uncharacteristic act of defecation. The reaction involving withdrawal of the paw is inhibited.

The exact same reaction is inhibited by preliminary stimulation of the oral receptors by water and the appearance of swallowing movements. Depression of the movement of the hind legs when the motor area of the cortex is stimulated appeared approximately 30 seconds after the beginning of swallowing movements and continued for some time, even after they had ceased.

In 1923, A. A. Ukhtomskiy used the term "dominance" for this phenomenon (from the Latin "dominare", to rule). Experimentally and theoretically, Ukhtomskiy substantiated his theory of dominance as the basic principle of the functioning of nerve centers.

Prolonged action of afferent impulses causes the appearance in the central nervous system of a "local focus of increased excitability." This focus can "attract" any waves of excitation circulating in the CNS, and its excitation is intensified because of them. The result is an inhibition of other reflexes, since stimuli that cause the development of these reflexes are now addressed to the dominant focus and are only capable of increasing its excitation.

"In conjunction with the formation of the dominant center, all of the excitation energy seems to flow to it from other centers and the latter are then inhibited due to inability to react." (Ukhtomskiy, 1923). /14

A focus of increased excitability can be formed under the influence not only of afferent impulses, but under the action of humoral factors as well: pharmacological effects of local chemical and ionic changes in the CNS and

substances introduced to the brain with the blood flow, as well as under the influence of hormones.

"The dominance of sexual excitement in a female cat, isolated from males during heat, is largely expressed in a pronounced and stable picture. The most diverse stimuli, such as the clatter of dishes on a table that has been set, calling the animal to its feed dish, etc., now do not evoke the usual meowing and lively begging for food, but only an intensification of the heat syndrome. Application of large doses of bromide preparations, even up to doses that cause bromism phenomena, cannot efface this sexual dominance in the centers. Even when the animal is lying completely relaxed on its side, various stimuli produce the same heat syndrome first of all. The established dominance is evidently very inert and permanent in the centers. Even a state of extreme fatigue still does not erase it. One gets the impression that dominance may become still more pronounced than normal when function of the CNS is retarded by the influence of fatigue or bromates, until it is finally extinguished" (Ukhtomskiy, 1923, p. 165).

The focus of increased excitability forming the dominant area does not arise at the cerebral cortex alone, emphasizes Ukhtomskiy. By allowing strychnine to act on a certain portion of the cerebellum of a spinal frog, one can create a stable local focus of increased excitability, at which any stimulation of the body begins to evoke not the reflexes typical for these stimuli, but reactions which are characteristic of centers possessing increased excitability.

"The rather stable excitation occurring in the centers at a given moment acquires the significance of a dominant factor in the function of the permanent centers; it accumulates within itself the excitation from remote sources, but inhibits the ability of other centers to react to impulses that are directly related to it" (Ukhtomskiy, 1925, p. 197-198).

"... We can create separate sensory and motor dominance in the spinal frog, subjecting the cerebellar areas to local poisoning, first in back (with

strychnine or phenol) then in front (phenol). The sensory dominance in the area of the rubbing reflex is expressed by the fact that although we have not stimulated the frog, it still rubs those areas of the skin which correspond to the poisoned segment of the brain: the reflex is splendidly coordinated, though not directed at the actual site of stimulation, but at the hyperesthetic zone of the skin. Figuratively speaking, we can say that the cerebellum /15 now interprets various stimuli as if they applied to the hyperesthetic zone. On the other hand, motor dominance in the rubbing region speeds up and intensifies the rubbing action, but is directed at the actual site of the stimulus. The centers project the stimulus completely correctly and only the motor accomplishment of the reaction is accelerated and irregular" (Ukhtomskiy, 1924, p. 191).

The ability to form dominant areas has also been mentioned in the nervous system of lower animals, for example, in the ganglia of the Gastropoda, the nerve elements of the marginal bodies of jellyfish, etc.

"Is it necessary to think of dominance as a topographically isolated point of excitation in the central nervous system? According to all the data, fully developed dominance is a complex of specific symptoms in the entire organism — in the muscles, in secretory activity, and in vascular activity. It is therefore rather a specific constellation of centers with increased excitability in different stages of the cerebrum and cerebellum, and in the autonomic system as well," writes Ukhtomskiy (1923).

But when does dominance cease to exist under natural conditions? After satisfying the biological needs that created it, i.e., as soon as its conditioned reflex activity is complete, or as soon as it ceases to be maintained by the action of afferent signals or humoral excitation (for example, the action of hormones). Dominance also disappears in those cases when a new dominance, incompatible with the first, arises in the centers under the influence of new factors.

"When dominance consists of a chain reflex aimed at a specific resolving action, the latter will be the end of the dominance. When swallowing, defecation, embracing have reached the final stage, it will be the end, but the endogenic end, of the corresponding dominance.

It is possible, however, for a new dominance to arise in the centers, which is incompatible with the first. The tendency toward restless locomotion in decerebrate animals does not lead to a decline of the dominance of rubbing. The development of a new dominance, one which is functionally incompatible with the first, marks the exogenic end of dominance.

It is also conceivable to have direct inhibition of dominance "in the brain" from the higher levels of the CNS (for example, from the cortex). We know that both inhibition and excitation from the cortex are especially powerful in their action on the spinal centers. It is remarkable, however, that the cortical effects that are obtained by stimulating the cortex with electrical currents and that are equally powerful in the conflict with spinal reflexes for control of skeletal muscles are themselves inhibited by the dominance of defecation and swallowing. It makes one think that direct inhibition from the cortex, directed at dominance "in the brain", is achieved with great difficulty. Of course, the cortex is more successful in its struggle with dominance, not attacking it directly, but creating a new compensatory dominance in centers." (Ukhtomskiy, 1925, p. 199) (author's italics).

Hence, under normal conditions the causes which prevent the existence of /16
a given dominance are diverse; first among them, obviously, is the signalling of the end of a given physiological act (reverse afferentation according to P. K. Anokhin, 1968). However, as soon as a given dominance has ceased to exist, for a long time the centers retain the readiness to produce it, and the entire reaction can arise under the influence of any one of the elements of the complex that produced it at one time.

In this revival of extinguished dominance, the critical role is played by the cerebral cortex. The cortex can revive an entire complex of nerve reactions that are characteristic of a given dominance, even in those cases when the direct causes that lead to the appearance of the dominance have ceased to operate.

The example of sexual behavior is characteristic in this regard. "The excitability of the sexual apparatus in the stallion always ceases after castration, if the animal has not experienced coitus prior to castration. Sexual dominance in such a case is simply erased from the life of such an animal. But if the stallion has experienced coitus before castration and the cortex has succeeded in linking visual-olfactory and somatic impressions with it, sexual excitement and attempts at intercourse will be renewed in the gelding in the presence of mares. The endocrine stimuli for the dominance have vanished, but it can still create its somatic components by purely nervous pathways, through reflexes along the cortical components" (Ukhtomskiy, 1924, p. 193).

Hence, the ability of the central nervous system to create a focus of dominant excitation can lead to sharp change and distortion of a number of stereotyped reflex actions, thereby ensuring the appearance of response reactions that are usually not characteristic of the given stimulus and cause the inhibition (and complete exclusion) of reflex reactions that usually arise under the influence of a given stimulus.

Since dominance is one of the basic principles of the function of the nervous system, it is understandable that this principle can appear not only in physiological, but also in pathological reactions, especially in those pathological processes in whose development and growth the nervous system plays an important role.

The Principle of Dominance and Pathological Processes

I. P. Pavlov repeatedly emphasized that the action of an "extreme stimulus" can lead to interruption of higher nervous activity, or neurosis. After the neurosis has been cured and the brain has been restored to function, the cortex may for a long time retain an isolated large area whose excitability markedly exceeds the excitability of other areas. The result is the development of a sort of latent pathological dominant focus.

In this case, even a weak stimulus directed to this focus can evoke inadequately strong reactions of the organism, to create a picture of neurosis /17 and interruption of higher nervous activity, and to cause a number of disorders affecting the internal organs and systems. The studies of K. M. Bykov et al. have made it possible to understand the mechanisms of disruption of vegetative functions in experimental neuroses and the development of "isolated large areas". Possessing the properties of dominance, such a focus attracts stimuli from other centers, which can lead to inadequate reactions with respect to the corresponding internal organs and systems and the development of pathological processes which in turn support the stimulus in these centers. The "vicious circle" is complete.

The development of the dominance in the nerve centers, as we know, is characterized by increased excitability of the dominant focus, strength of stimulus, capacity for summation, ability to attract stimuli and, because of the latter, to increase its own characteristic stimulus and to inhibit other reactions of the organism. If these characteristics of the dominant focus provide for better adaptation of the organism to environmental conditions in the normal state, the development of pathological dominance often disrupts those adaptative reactions and furthers the intensification and seriousness of many pathological processes, and can lead to the appearance of relapses that develop in accordance with the mechanism of so-called "trace reactions".

The studies of A. D. Speranskiy et al. revealed that the production of pathological states by the mechanism of "trace reactions" is also possible under the influence of nonspecific stimuli, which were not linked previously with the action of pathogenic agents. The active stimulus in this case must be "extreme". Thus, a powerful, nonspecific stimulus to the nervous system, a so-called "second blow" according to A. D. Speranskiy (for example, injection of turpentine or croton oil into the trunk of the sciatic nerve) in the case of an animal which in the past has been subjected to experimental tetanus (produced by the injection of tetanus toxin), produced the development of the picture of a tetanus relapse. An animal of this sort can die from the symptoms of tetanus, although no tetanus germs are present in its body. Similar experiments succeeded in creating in experimental animals the symptoms of "secondary poisoning" with benzene, relapse into various forms of nervous dystrophy, disruption of kidney function and other pathological processes. It should be emphasized that the mechanism of "second shock" can produce not only the phenomenon of "breakdown" but also latent reactions of the organism, for example, leucocytosis, increased titre of specific antibodies, etc.

The appearance of relapses of an illness following the action of extreme stimuli shows that the cure does not always mean complete liquidation of all changes that occurred during illness. It can occur even in the compensation /18 of disturbances by means of development of new conditioned-reflex reactions, i.e., new relationships within the nervous system. The leading role in these compensatory processes is assigned to the cerebral cortex (Asratyan, 1953, 1959). The "second shock" may be the cause of an interruption of this compensation and a return of the pathological process that existed earlier. The mechanisms for development of pathological processes after the "second shock" require further study. We know that pathological states are very hard to reproduce on the basis of the type of "trace reactions". They can arise and establish themselves only under certain conditions that are especially unfavorable for the organism and which lead to a weakening of the nervous system.

Ideas regarding the development of pathological dominance in centers formed the basis of the theory of the pathogenesis of hypertonic illness and other ailments that was developed by clinicists (Lang, 1950; Myasnikov, 1954) and physiologists (Magnitskiy, 1952; et al.).

Hence, the ability of the nerve centers to create dominance plays an important role in the development of many pathological processes. We can therefore imagine that in order to prevent these processes it is important to know how to inhibit this pathological dominance. As we know, prevention of dominance is possible under the influence of signals indicating the end of the auxiliary biological act creating it, due to cessation of the action of the stimulus that caused the dominance, by direct cessation (inhibition) of impulses from the cortex and the creation of a new dominance in the centers that concurs with the given dominance.

Direct inhibition of the dominance, "inhibition in the brain", is not a simple problem for the cortex, as Ukhtomskiy has repeatedly emphasized. However, in the case of general inhibition of the central nervous system, the dominant focus as a rule is excluded by the latter and therefore an attempt to use soporific or even narcotic agents to combat pathological dominance may lead to opposite results — inhibition of all other forms of activity of the central nervous system and retention of relatively stronger dominance against this background.

The "simplest" and "most economical" way to inhibit dominance, according to Ukhtomskiy, is to create another type of dominance in the centers, i.e., to create a second dominant focus, incompatible with the first, which will lead to the inhibition of the original dominance. We can therefore imagine that the removal of pathological dominance can obviously be accomplished according to the principle of negative induction, that results in a process of "external inhibition", which Pavlov considered to be the most economical form of inhibition in the central nervous system. It is precisely these views of Ukhtomskiy and Pavlov that we have tried to use in inhibiting

pathological dominance with the aid of rather strong supplementary nonspecific stimuli (Kositskiy, 1954, 1955, 1956a, 1956b, 1962).

CHAPTER II.

INHIBITION OF PATHOLOGICAL PROCESSES UNDER THE INFLUENCE OF SUPPLEMENTARY NONSPECIFIC STIMULI

/19

Many authors have described the possibility of arresting many pathological processes by using supplementary nonspecific stimuli. Later on, in discussing Selye's concept, we will give a survey of the literature. In the present chapter we will limit ourselves only to materials from our own experimental studies regarding the influence of supplementary nonspecific stimuli on certain pathological processes. The supplementary nonspecific stimuli that we used in our different series of experiments were either a pulsed electric current or the injection of turpentine or formalin.

We know that electric current is by nature the greatest physiological stimulant, since within certain parameters it causes changes in the organs and tissues which are analogous to those which occur when the latter are naturally stimulated; it can be switched on and off at any time during the experiment and is easy to adjust as far as frequency and voltage are concerned. Electric current is widely used as a stimulus to produce a dominant focus of stimulation in the CNS. I. A. Vetyukov (1926) presents data indicating that dominant foci in the spinal cord of the frog are readily developed at a slow stimulation frequency (for example, 80 impulses/min), while dominance does not appear at higher stimulation frequencies (40-60 impulses/sec.)

Electric current is often used as one of the "stressors", producing its effect through the CNS (Mikhaylova, 1955; Eskin, 1957; Redgate, 1960).

We also used electric current as a supplementary nonspecific stimulus in our experiments. An induction coil was used as the current source in several experiments; voltages of 2, 4 or 5 volts were supplied to the primary winding

from the line voltage through a transformer. The current was applied after passing through a breaker on the coil, which determined a stimulation frequency of 50 Hz. In other experiments, the source of pulsed current was an electronic stimulator which made it possible to vary the frequency and amplitude (strength) of the current at the output within wide limits. The electrodes were placed on the thigh muscles or (in some experiments) on the peritoneal wall of the animal. The current intensity was selected individually and was rather high (3.5 to 5 mA) but not extreme, in order not to evoke motor reactions on the part of the animals. When subjected to the action of the current, the animals, which were fastened to the table, usually lay quietly and were somewhat passive.

Turpentine. As we know, turpentine has a powerful local stimulating effect, so that it has been used for a long time in medical practice. As /20
far back as the 16th century, Ambrose Paré was using turpentine in his ointment to cure wounds. Turpentine is now used in several ointments, which (in A. V. Vishnevskiy's opinion) have favorable trophic effects, stimulating the nerve elements of the tissue. Purified turpentine is used in medical practice for inhalation in the case of saprogenic bronchitis, pulmonary gangrene, etc., (and also as a "distracting" medium in many diseases: rheumatism of the joints, puritis, myosites, neuralgia, etc.). Turpentine is partially oxidized and combined with glucuronic acid in the organism (man and animals), and is excreted in the form of this complex. When injected subcutaneously, turpentine acts as a strong stimulus which causes nonspecific turpentine inflammation, accompanied by significant changes in the functions of many organs. There is a sharp increase in the secretion of gastric juice, spontaneous excretion of pancreatic juice, stimulation of secretion from the sweat and bronchial glands, and increased diuresis.

Turpentine has been used as a strong stimulant by several experimenters to obtain pulmonary edema. Thus, when turpentine is injected subarachnoidally, stimulation of the central nervous system causes the appearance of "hemodynamic" pulmonary edema (Chernukh, 1950, 1952, 1954; Sarkisov, 1952; Gamble and Patton, 1951; Speranskiy, 1942).

A. M. Chernukh (1950, 1952, 1954) produced pneumonia and pulmonary edema in rabbits and guinea pigs by injecting turpentine beneath the epineurium of the vagus nerves. The significant decrease in the changes in the lungs when turpentine is injected into previously novocainized nerves indicates the causative role of nervous stimulation.

Hence, turpentine, as a supplementary nonspecific stumulant, not only can produce, but can also prevent the development of pathological processes. It was used for this purpose in our experiments. Turpentine was injected subcutaneously or intraperitoneally prior to the action of pathogenic stimuli.

Formalin. The other supplementary stimulus which we used in our experiments was formalin. We know that formalin was widely used by Selye and other investigators as a powerful "stressor". Selye (1938a) prevented the development of adrenalin pulmonary edema by giving three subcutaneous injections of 0.5 ml of 4% formalin solution. By itself, formalin (like turpentine) has a stimulating effect on animals, but formalin is less toxic for the organism. It is excreted through all mucous membranes (especially the respiratory pathways). The excretion of formalin takes place much more rapidly than the excretion of turpentine.

The present chapter describes the results of an investigation of the effect of these supplementary nonspecific stimulants on the development of certain pathological processes: frostbite, tuberculin allergic reactions, reactions to air embolism, adrenalin pulmonary edema, etc.

These pathological processes were to a certain extent selected by us at random. We wanted to study pathological processes that were known to be quite different from one another and whose pathogenic mechanisms were especially specific and unique.

Since we do not have space within this small book to give exhaustive detail regarding the pathogenesis of each of these processes, we will limit ourselves only to the participation of the nervous system in their development.

Frostbite /21

The problem of frostbite, as we know, is one of the most serious problems in world medicine, especially in the armed forces. According to the data of many authors, frostbite is the cause of as much as one sixth of all hospital casualties in the armies of the world. The death of tissues following frostbite leads to crippling and mutilation. The causes of the development of tissue necrosis in frostbite are not completely clear. The idea that the cause of tissue death in frostbite is the direct action of cold on cells is not supported by all the facts. We know that frostbite and tissue death can arise under the influence of temperatures that are much higher than zero, at +5° or even +10° ("trench foot"), when there is no question of freezing.

We also know that the cells in tissue which has been isolated in vitro will survive complete freezing (i.e., the same degrees of cooling which would lead to the death of these same tissues in an intact organism). The process of tissue death in the intact organism does not begin immediately when cold begins to act, but much later. However, even when the temperature drops as low as -183° and is allowed to act for 20 seconds to 5.5 minutes, it does not produce direct death of the tissues (Komarov, 1949). These facts indicate that the action of cold on the tissues of an intact organism is followed by the development of some kind of changes which then lead to the death of these tissues.

The pathogenisis of frostbite has been investigated in detail in monographs by T. Thomas, Ya. Ar'yev (1940), G. L. Frenkel' (1923), N. I. Gerasimenko (1950) and Barton and Edholm (1957).

The Role of the Nervous System in the Pathogenesis of Frostbite

The significant role played by the nervous system in the development of many pathological processes leads us to suggest that the development of tissue

necrosis in frostbite may be related to a disturbance of the nervous regulatory effects and to a development of what I. P. Pavlov in his time called "negative trophic reflexes".

The validity of this assumption is supported by the phenomena associated with the death of tissues not only in the frozen extremities themselves, but in tissues in the vicinity not subjected to the action of cold. This is indicated by the experimental studies of V. N. Chernigovskiy and N. P. Kurpatova (1941) who showed that when one extremity is cooled and frozon, blood circulation drops on both the frozen side and on the other side as well. K. M. Bykov (1942) stressed the reflex nature of this phenomenon, stating that therapeutic measures to be taken for frostbite must be directed not only at the frozen extremity, but also at the opposite one.

The role of the nervous system in frostbite phenomena has been indicated /22 in many other observations.

V. M. Osipovskiy (1953), in treating frostbite in human beings, noticed the good therapeutic effect produced by the application of a lumbar novocain block.

G. A. Orlov (1937), in his experimental studies on white rats, showed that the use of a circulatory novocain block 6-8 hours after frostbite prevents the development of tissue necrosis when the tail has been cooled in chlorethylene. A circulatory block applied prior to frostbite (or 18-24 hours afterward) failed to prevent the development of necrosis. A block applied 20-24 hours later even accelerated the development of necrosis and the loss of the necrotized tissues.

Orlov's work was published in 1937 in France, and French surgeons headed by Leriche commented on it in a seried of similar studies which were published in 1938-1939.

M. M. Sandomorskiy (1941), S. N. Davydenkov and A. F. Verbov (1943) described neuritis in frostbitten individuals with disorders in trophics and sensitivity (especially neuralgia), which were retained for a long time even after the frostbitten tissues were revived.

N. I. Kukin (1941) presents clinical data on the favorable therapeutic effect of novocain block in curing frostbite. It should be mentioned that this author observed only those stages of frostbite in which necrosis had already developed.

N. N. Burdenko (1942), on the basis of data from experimental and clinical studies, stated that an important role in the pathogenesis of frostbite is played by overstimulation of the sympathetic nervous system and the development of hyperadrenalemia in it.

D. I. Panchenko (1943, 1946), in a morphological study of the nerve trunks of frostbitten extremities of human beings who had died of infection, noticed degenerative changes in the nervous tissue in areas which were not subject to the direct action of cold.

I. P. Chulkov (1949) was able to confirm experimentally the data of G. A. Orlov regarding the favorable effect of a novocain block and showed that cutting the spinal cord at the level of the lumbar vertebrae prevented the development of tissue necrosis. Anesthesia had the same effect. On the other hand, cutting the femoral or sciatic nerves caused the development of more extensive gangrene of the shin and foot and the death of the animals.

N. P. Golysheva (1941) reached similar conclusions, noting an increase in necrotic processes when the ears of rabbits were frozen following de-sympathetization.

Hence, in many instances effects on the nervous system prevented the /23
appearance of necrosis in frostbite. In other observations, however, similar effects accelerated the development of necrosis. In both cases it

was found that the nervous system did have an effect on the development of the process of the death of the frostbitten tissues.

One might think that the direct action of cold produces significant changes in the metabolism and the physical and chemical state of the affected tissue. These changes are not always sufficient of themselves for direct development of irreversible necrotic processes; in an in vitro culture, the death of tissue following frostbite is not a necessary consequence. In an intact organism, however, the serious changes which occur under the influence of cold apparently lead to an excessive stimulation of receptors (and possibly nerve fibers as well). We can imagine therefore that after restoration of nervous conductivity at the moment of heating, the frostbitten tissue becomes a source of strong painful sensations. Later subjective feelings of pain are obtuse, but the frozen tissue obviously continues to be a source of "extreme stimulation" of the nervous system for a long time still.

The prolonged action of "extreme stimuli", which can be physical and chemical changes in the frostbitten tissue, can lead to pathological congestive inertia of the affected centers, which receive signals from this focus. The excitability of these centers obviously increases sharply in comparison with others; they become the site of attraction of other impulses, forming a pathological dominant focus. The increased circulation of impulses between this focus and the frostbitten tissues can cause the development of a "vicious circle", which accompanies the appearance of trophic disturbances in the development of tissue necrosis in the frozen area (Kositskiy, 1956).

It is understandable that the causes of the development of tissue necrosis cannot be attributed to the development of a "pathological dominant focus". The circulatory pathways are disturbed in the frozen area, there is a change in the permeability of the vascular walls, oxygen starvation develops, the nature and intensity of metabolism change, etc., i.e., a number of typical pathological processes arise. At the present time, the pathogenesis of frostbite has still not been thoroughly investigated. Our

problem consisted only in considering the possibility of the participation of the nervous system in the development of tissue necrosis in frostbite.

Animals in various stages of post-natal ontogenesis were a suitable object for studying the role of the nervous system in the development of tissue necrosis in frostbite.

As we know, puppies and kittens are born blind. Until their eyes open, a number of nerve regulator mechanisms do not function in these animals. /24
This fact is indicated by the absence of conventional reactions with adequate stimulus of the vascular reflexogenic zones, tonic effects of the centers of the vagus nerves on the heart, constant muscle tone, low lability of neuromuscular apparatus and impossibility of assuming a standing posture. Regulation of a number of vegetative functions in such animals is accomplished to a large degree by humoral regulatory mechanisms, etc. (Orbeli, 1934; Arshavskiy, 1936, 1967; Yankovskaya, 1938; Arshavskaya, 1943, 1946; Kositskiy, 1949b, et al.). The opening of the eyes leads to a sharp increase in the flow of impulses reaching the CNS; this causes a rapid increase in its tone and the abrupt inclusion of a number of nerve mechanisms for regulation which did not function earlier.

We can therefore assume that a study of the development of tissue necrosis during frostbite in the early stages of post-natal ontogenesis (before and after opening of the eyes) might give valuable additional information regarding the participation of neuroregulatory mechanisms in this process.

In this regard, we studied the progress of frostbite in kittens ranging in age from 1 day to 16 days. Freezing the ear with ethyl chloride in 16-day old kittens caused development of necrotic inflammation, tissue death and loss of the ear at the base, with formation of a stump.

When the same freezing with ethyl chloride was used on the ears of kittens one day old, edema and inflammatory phenomena were much less

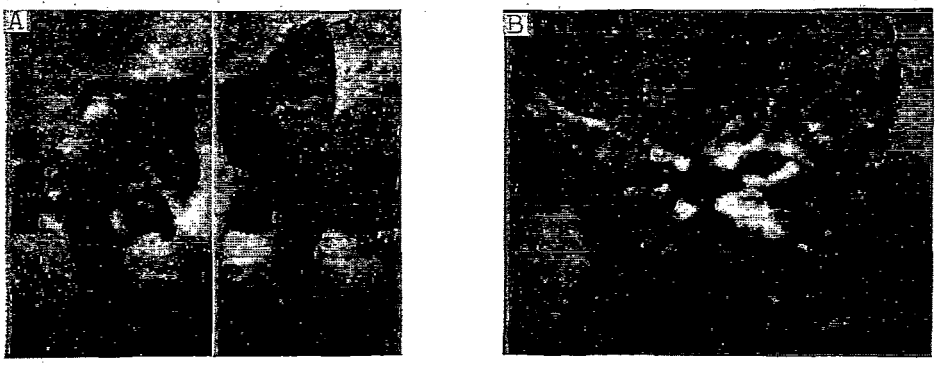

Figure 1. Kitten, after freezing the right ear with ethyl chloride.

A - Frozen when 16 days old: amputation stump of necrotized ear; B - Frozen when 1 day old; no necrosis.

pronounced than in the 16-day old kittens; after edema subsided, tissue death did not occur. Subsequently, there was only a very slight stunting of the growth of the frostbitten ear (Figure 1). /25

Hence, we did not observe the development of tissue necrosis following frostbite during the first days of post-natal ontogenesis; this may have something to do with insufficient functioning of neuroregulatory mechanisms during this period. However, we cannot exclude the possibility that this development is linked with characteristic actions of humoral regulatory mechanisms or a change in the properties of the tissues themselves at this age.

Hence, the following experiments were conducted only on adult animals.

In one version of the experiment, we studied the influence of anesthesia on the development of necrosis in the ears of rabbits and cats, frozen with ethyl chloride. The control animals (7 rabbits and 2 cats) had their ears frozen with ethyl chloride, which led to pronounced hyperemia and edema of the ear on the following day; it increased later on. The red coloration of the

hyperemia changed to blue, sometimes with a violet tinge. After 8 to 10 days, there was wet or dry necrosis, which terminated 20-30 days later in loss of the ear and development of a granular stump. The development of necrosis in rabbits and cats was the same within general limits (Figures 2 and 3).

Thirteen other rabbits and two cats, immediately after having their ears frozen in this manner, were anesthetized by intraperitoneal injection of 2.0 to 3.0 ml of 10% sodium evipan. The shortest duration of anesthesia in this group of experiments was 4 hours, while the longest was 2-1/2 days. During anesthesia, hyperemia and edema of the frostbitten ear developed as usual. However, these phenomena were less pronounced than in the control animals. Later on, four of the animals failed to develop tissue necrosis after edema had subsided, or else it developed much later and involved only the edges of the ear. Seven animals in this series later developed gangrene of the ear, with formation of a stump; four of the animals died on the second or third day after they were given the anesthetic, and we were unable to follow later results. In these cases, however, we noticed significantly less developed edema and inflammatory phenomena in comparison with the control animals for similar periods of time.

Consequently, the administration of a large dose of narcotic following frostbite led to inhibition of the inflammatory necrotic reaction and sometimes completely prevented tissue necrosis (Figures 2 and 3).

In subsequent experiments on seven rabbits, we studied the effect of continuous 2- and 3-day anesthesia. The methods of inducing frostbite were the same as those in the preceding experiments. After freezing the ear, we anesthetized the rabbits. For 2 days the animals received intraperitoneal injections of 1.0 to 2.5 ml of 10% sodium evipan whenever necessary so that they were kept in a continuous deep sleep for 2 and 3 days. In this group of experiments, five rabbits died on the 3rd day from an overdose of anesthetic. However, during sleep the edema, hyperemia, and cyanosis of the ear were much less pronounced than during the same period of

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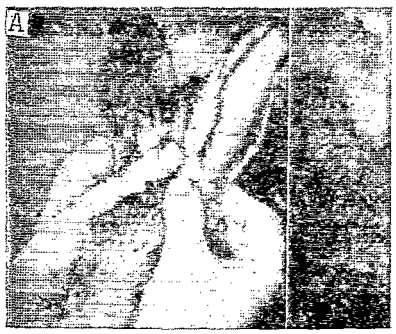

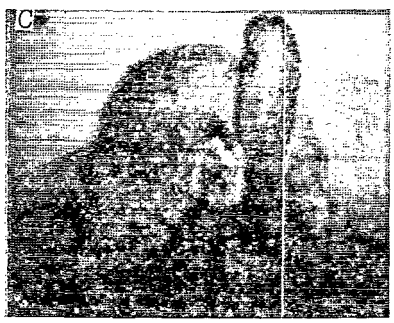

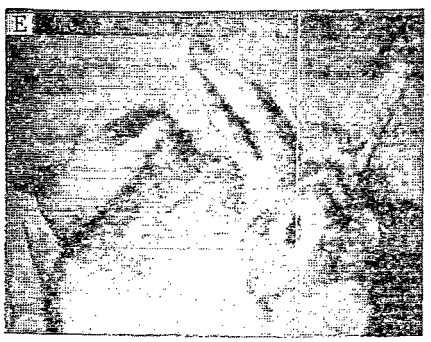

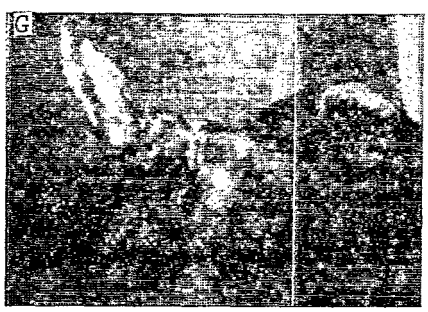

Figure 2. Rabbits, following freezing of the ear with ethyl chloride. A - Control, 7 days after freezing; necrotic loss of right ear; B and C - Same rabbit, 30 and 95 days after freezing (dry necrosis), (B) and autoamputation (C) of the ear; D,E, F - Rabbit in which, after freezing the right ear, prolonged narcotic sleep was induced: after 7 days (D), 30 days (E) and 95 days (F), there was no necrosis; G - Amputation stump of left ear in the same rabbit following freezing without narcosis.

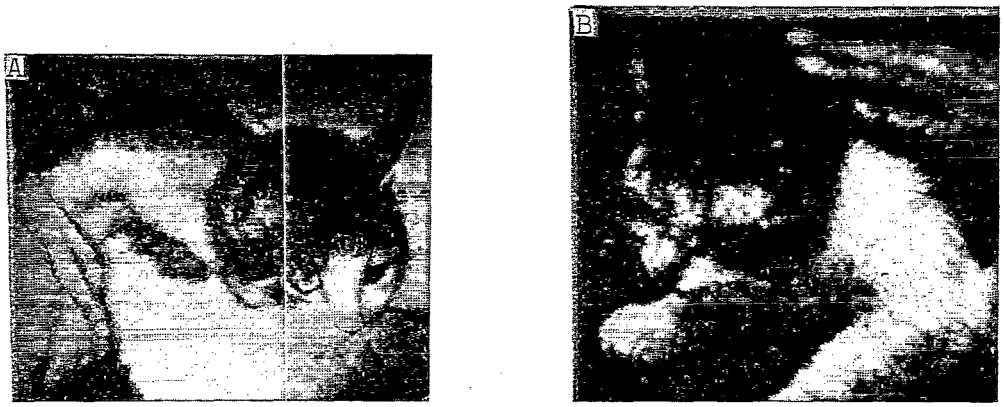

Figure 3. Cats, after freezing right ears with ethyl chloride. A - Amputation stump of ear following total necrosis (control); B - Cat in which, after freezing the right ear, prolonged narcotic sleep was induced. Only slight necrosis of one edge of the ear has developed; the ear as a whole was retained.

time in control animals. In one case, the anesthetic was administered at long time intervals, and the rabbits were awake during the period between injections. Before awakening them, we administered a novocain block at the base of the ear with 0.25% novocain. The inflammatory symptoms were much less pronounced than in the controls; necrosis developed two weeks later and involved only the tip of the ear (and not the frozen tissue, as in the control animals). In one case, regardless of the high doses of narcotic substances, the anesthesia in the rabbit was very low; the animal was partially awake, raised its head, sat up, and so on. In this experiment there was a marked picture of necrotic inflammation with wet gangrene on the ear and death of the animal a week after the frostbite.

Hence, we found that deep prolonged anesthesia arrested development of the inflammatory necrotic processes in frostbite, while light anesthesia did not arrest tissue necrosis.

These experiments are a confirmation of the theory that the nervous system plays an important role in the development of necrotic processes in

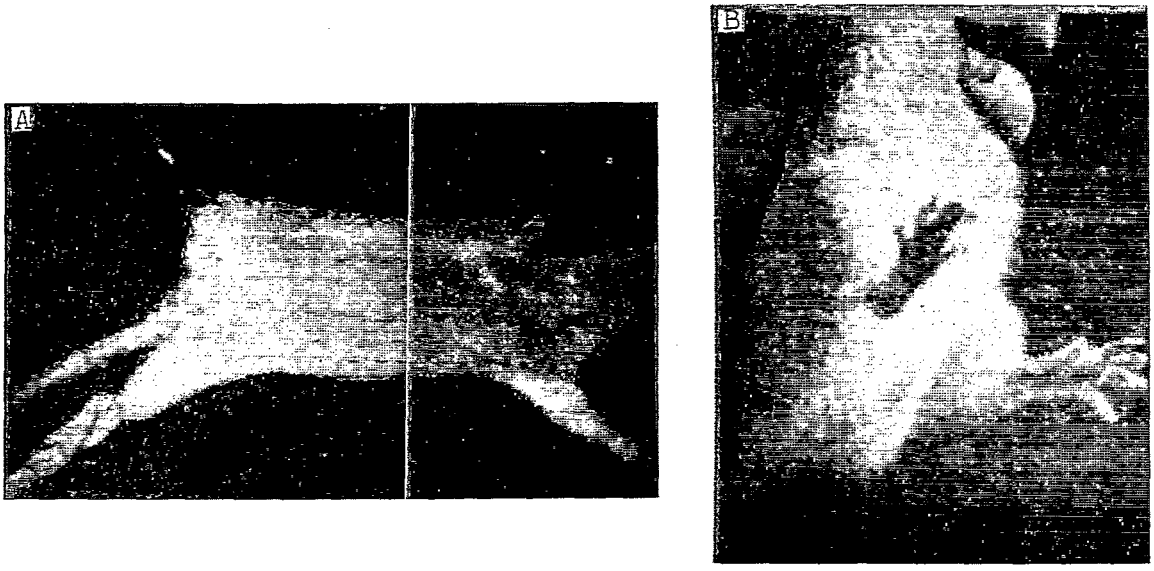

Figure 4. Rats, after freezing right feet with ethyl chloride. A - amputation stumps of right feet after necrosis; B - Rat subjected to 24 hour action of electric current while freezing right feet; no necrosis.

frostbite. Having confirmed this fact, we attempted to study the effect of supplementary nonspecific stimulants on the development of tissue necrosis /28 in frostbite.

Course of Processes in Frostbite Under the Influence of Supplementary Nonspecific Stimulants

In control experiments performed on 20 white rats, tourniquets were applied to the animal's thighs, after which severe frostbite was induced in the feet with ethyl chloride; the tourniquets were removed after 5 minutes. In all cases, pronounced edema and cyanosis of the frozen feet appeared on the following day. The feet became bluish-violet in color. On the following days, wet or dry gangrene of the tissues developed, with loss of feet on the 8^{th} to 14^{th} day after freezing (Figure 4a).

In the case of ten rats, platinum electrodes were applied to the muscles of the left thigh, through which electric current could be passed from a

Dubois-Raymond coil. The current strength was selected so that the animals were in a state of stupor (with the distance of the coil equal to approximately 14 cm and the voltage in the primary winding equal to 2 V; for more details see pages 70 - 71)*.

We caused trostbite in the right foot in the manner described above; the animals were subjected to the action of continuous faradic current of fixed intensity during the entire period of exposure to frostbite and for 24 hours thereafter. Two out of the ten animals were subjected to continuous current for 48 hours after being frostbitten. Edema was significantly less in all of these animals on the day following frostbite than it was in the controls. Moreover, four of the rats did not develop necrosis of the foot and did not lose the limb. After cessation of edema and desquamation of the skin, the appearance of the foot was completely normal and the animals used it in the usual manner for locomotion, moving over the walls and ceiling of the cage, grasping the screen mesh with all four toes. Two other rats developed gangrene of the toes alone at much later dates than the control animals; they subsequently lost these toes, but the rest of the foot tissue was retained and continued to function (Figure 4b). Four rats (including the two that were exposed to current for 48 hours) died one day later (two of them after the current was switched off). The edema in the frostbitten extremities of these animals was significantly less than for the same period of time in the controls. Two rats which were exposed to the current for 24 hours developed conventional gangrene and lost their limbs, while necrosis and loss of the limb occurred much more rapidly than in the control animals (the tissues decomposed on the 4^{th} and 5^{th} days following frostbite).

It is obvious that the action of the supplementary nonspecific stimulus caused significant changes in the development of the necrotic process. In the majority of the animals we succeeded in retarding or preventing the development of necrosis. In other experiments, however, the necrosis and decay of tissues were accelerated. In both cases we may properly speak of the participation of the nervous system in the development of necrotic tissue processes in frostbite. /29

*Translator's note: This corresponds to English pages 88 - 90.

The exclusion of inhibition of reflex mechanisms may prevent necrosis of frostbitten tissues. However, when a conventional anesthetic is given, it is necessary to have a very deep anesthetic sleep lasting several days, which in itself constitutes a danger to life. It is less dangerous for the organism to have a process of external inhibition and the formation in the CNS of a new focus of dominant stimulation. This can be a "nonspecific" focus, which arises under the influence of rather strong but indifferent (nonpathogenic) stimuli. A "nonspecific" dominant focus of this kind can /30 produce inhibition of other centers and reflex reactions of the organism, including reactions which are involved in the development of tissue necrosis during frostbite.

The model of the pathological process described above turned out to be not very valuable for this purpose. The process of tissue necrosis in frostbite is complex and prolonged. It passes through a number of stages during each of which the nature of the participation of reflex mechanisms and their individual importance vary. It was therefore necessary to find other models of the pathogenic reactions which were more suitable for our purposes.

Tuberculin Allergic Reactions

We now know that the development of immunity reactions in the organism are subject to the regulatory effect of the nervous system. However, the concrete mechanisms of this effect and the concrete forms of participation of the nervous system in the regulation of immunity processes require further investigation.

A. D. Speranskiy and his school hold the opinion that the infection process is essentially a reflex process, and that there are receptors in the organisms which receive specific antigen stimuli. The problem for the investigator is to compile the "topographic chart" of these receptors for a fine control of the pathological process (Durmishyan, 1952).A. N. Gordiyenko (1954) also feels that the mechanism of the development of specific immunity

reactions is reflex in nature (i.e., there are specific receptors which detect the action of antigens.)

However, the majority of investigators do not share this viewpoint. A. D. Ado et al. showed (1952, 1957, 1962) that antigens are "extreme stimuli" of the nervous system and of receptors in particular, and that the development of an allergy is accompanied by a rise in the sensitivity of the receptors to the action of the antigens. This increase in sensitivity, in Ado's opinion, is not specific for a given antigen and extends to the action of other stimuli as well. In contrast to the authors mentioned above, P. F. Zdorovskiy (1960, 1963) feels that the primary point of application of antigens is the tissue and that the specific nature of the immunity reactions depends on the specificity of the direct tissue reaction. In the author's opinion, only the regulation of the intensity and degree of this specific tissue reaction depends upon the nervous system, i.e., the nervous system regulates the quantitative but not the qualitative aspect of the immunity reaction. In the following, we shall discuss this problem in greater detail, using the model of tuberculin allergic reactions. /31

The Role of the Nervous System in the Development of Tuberculin Allergic Reactions

We know that the total resistance of the organism with respect to tubercular infection and the degree of severity of the local specific tissue reactions depend upon the functional state of the nervous system. However, the problem of how the latter affects the development of a tubercular process is a very complex question and one which has not been thoroughly investigated.

Even in the course of studying one aspect of this problem (to wit, the role of the nervous system in the development of tuberculin allergic reactions), completely different and often mutually exclusive viewpoints have arisen. In the course of studying this disputed problem, many facts have

been accumulated which directly or indirectly indicate that the nervous system has an influence on the development of tuberculin allergic reactions.

Thus, the experimental studies of M. V. Trius and G. I. Kositskiy (1951), R. O. Drabkin and Ye. F. Kuchak (1952) and V. V. Arkimovich (1953) showed that anesthesia inhibits the development of cutaneous tuberculin reactions (Mantu reactions) in experiments on guinea pigs. M. D. Shkol'nikova (1954) stated that the specific reactions of the blood are reduced if intramuscular injection of tuberculin is performed in a denervated or novocainized area.

To study the role of the nervous system in the development of tuberculin allergic reactions, G. I. Kositskiy and T. N. Yashchenko (1956) conducted a number of special experiments on guinea pigs.

Tuberculin (ATK) was injected subcutaneously (0.1 ml in a 1:10 solution) into 16 guinea pigs which were sensitized with BTsZh vaccine; 8 of these were placed under urethane-veronal anesthesia before the tuberculin was injected; this anesthesia lasted 15 to 16 hours after the tuberculin was injected.

The same method was used in subsequent experiments. It was found that the allergic reactions were much less pronounced in the sleeping animals than in those that were awake.

In other experiments, tuberculin was injected intraperitoneally (0.1 ml, /32 undiluted) into 16 guinea pigs sensitized with BTsZh vaccine; 8 of these were anesthetized. The animals which did not die of tuberculin shock were sacrificed 24 and 48 hours after tuberculin was injected. The degree of hyperemia of the peritoneum was evaluated, as was the nature and amount of the exudate. In the sleeping animals, the reactions proceeded more slowly than in the animals which were awake; however, after the animals awakened, the reaction developed more rapidly than it had up to this time in the controls. We had not observed this effect in our previous experiments. It is possible that this had something to do with the fact that in these experiments we gave

a 100-fold larger dose of tuberculin, and it could not be resorbed until the animals awoke.

Later, tuberculin was injected intraperitoneally in the same doses into 23 guinea pigs one month after infecting them with a virulent culture (Bov - 8, 0.01 mg); 15 guinea pigs were anesthetized using the same method and 8 served as controls. In the case of virulent infection, the difference between the effect of tuberculin on the animals in the experimental groups and control groups was less pronounced than in the case of vaccination with BTsZh; 10 out of 15 guinea pigs died showing symptoms of "tuberculin death during anesthesia. However, the local inflammatory reaction of the peritoneum in the anesthetized animals was still less than in the controls. One month after virulent infection, twelve guinea pigs were given a subcutaneous dose in the rear foot, 2.0 ml each of 0.25% novocain. Five to ten minutes later, 0.1 ml of 1:10 tuberculin was injected subcutaneously into the zone of novocain infiltration and into a front (control) foot. Novocain in the same dose was injected twice more into the infiltration zone after 2 and 2.5 hours. After 24 hours, the allergic reaction failed to appear in the front and rear paws. After 48 hours, five of the animals developed tuberculin reactions in the front paws. As before, the rear paws showed no tuberculin reaction in the zone of novocain infiltration.

In the case of 8 guinea pigs, the spinal cord was completely severed in the lumbar region following virulent infection. Tuberculin was administered subcutaneously into the rear and front (control) feet. A sharply positive reaction appeared in the front paws, while the rear ones ("denervated") showed no allergic reactions.

The data obtained as a result of all these experiments indicate participation of the nervous system in the development of tuberculin allergic reactions. Prolonged anesthesia, novocainization and cutting of the spinal cord all inhibit development of local allergic reactions. Our co-worker, A. I. Volegov (1965), reached similar conclusions in his study of tuberculin reactions in human patients ill with tuberculosis.

Volegov used a subcutaneous tuberculin test in his work (Mantu reaction). Patients with pulmonary tuberculosis received with the tuberculin (mixed with it) vegetropic substances (atropine, redergam, proserine, ephedrine and also an antihistamine preparation, dimedrol) in doses equal to 0.01 of the therapeutic dose of each of these substances when administered subcutaneously. The atropine, redergam and dimedrol were given mixed with tuberculin, not only separately, but in paired combinations with one another. We also studied the influence of a combined solution of all three of these substances. We set up control studies to check the retention of certain specific properties of these substances in the combined solutions.

In studying the Mantu reactions in 404 tubercular patients, we found that /33 atropine, redergam and dimedrol inhibited the development of cutaneous tuberculin reactions in various forms of tuberculosis of the lungs in the phase of infiltrative flare. The joint action of any two of these substances had a still more pronounced inhibitory effect. At the same time, however, proserine (in some cases, ephedrine) intensified the tuberculin allergic reactions. In similar studies conducted in patients in the course of resorption of the tubercular process, it was found that the inhibitory effect of the above vegetropic substances on the tuberculin reactions was much weaker. Hence, there was evidence of action of the vegetative nervous system on the tuberculin allergic reactions and it appeared that the degree of development of tuberculin allergic reactions is dependent on the state of the nervous system. This is also supported by the results of other clinical observations.

However, none of the studies described above, which show in one way or another the influence of the nervous system on the development of tuberculin allergic reactions, allows us to draw any conclusions as to whether these effects are specific or nonspecific.

As we have already pointed out, a number of investigators have voiced the opinion that tubercular antigen is a specific stimulant for the nervous system and that the development of the tuberculin reaction is a reflex type

of response. G. S. Kan (1954) feels that tubercular antigen is a specific stimulant for the interoceptors. A. Z. Sigal found that the development of tuberculin allergy in guinea pigs is accompanied by the development of an increase in the specific sensitivity of the receptors of the carotid sinus to the action of tuberculin. F. A. Levtova (1954) came to the conclusion that the action of tuberculosis antigen on the chemoreceptors of the intestine is specific. On the basis of these data, G. S. Kan (1955) developed the reflex theory of pathogenesis of tuberculosis, assuming that the action of the tubercular antigen on the tissue takes place through interoceptors (i.e., it is accomplished with the aid of the nervous system).

However, these investigators used Koch's Old tuberculin (ATK), whose production technology is such that it contains (along with the specific antigens) a large amount of nonspecific products (evaporated bouillon and the products of its breakdown and decay); the amount of the latter is considerably in excess of the amount of tuberculosis antigens per se. We cannot exclude the possibility that these products, which have no relationship to the tuberculosis antigen, have a pronounced neurotropic effect and are able to produce considerable changes when they are introduced into the organism. However, the authors cited above did not pay any attention to the possibility of a stimulating effect by these nonspecific substances. It is clear that the results they obtained require further experimental confirmation. It is /34 necessary to determine first of all the degree to which the changes that develop in the organism following the injection of ATK may depend on the specific action of tuberculosis antigen and the extent to which they may be caused by the action of the nonspecific products which are found in ATK.

Our experiments were based on intact guinea pigs and white rats and on animals which had been sensitized to the action of tuberculin (vaccinated with BTsZh).

The test involved changes in the arterial blood pressure and respiration. Tuberculin was injected into the jugular vein in different strengths. To study the direct action of tuberculin on the nervous system, it was injected

into the cerebrospinal fluid by suboccipital puncture. As indicated by the data of L. S. Shtern (1960), Ya. A. Rosin (1961) and other investigators, this makes it possible to apply the substance directly to the nerve centers, so that in many cases reactions develop in the organism which are opposite to those which are produced by intravenous injection of the same substance. It is very important that an opposite reaction of the "center" and "periphery" is observed only with the action of substances which are specific stimulants for the nervous system. Substances which are indifferent in regard to the nervous system do not produce opposite reactions when given by these different methods of injection. We used these facts to analyze the action of tuberculin on the nervous system.

We measured arterial pressure in the carotid artery in anesthetized white rats and guinea pigs (using a mercury manometer), as well as respiration (using a Marey tambour). Tuberculin solutions (in physiological solution), heated to body temperature in concentrations of 1:100, 1:10 and undiluted, were injected in amounts of 0.3 to 1.0 ml intravenously and into the CSF by means of a suboccipital perforation in amounts of 0.1 to 0.05 ml. The controls received equal amounts of physiological solution. The experiments used 48 animals (40 white rats and 8 guinea pigs); of these, 23 rats 4 guinea pigs were intact (non-vaccinated), while 17 rats and 4 guinea pigs were vaccinated (by injection of BTsZh vaccine).

The vaccinated animals were brought into the experiment at a time when the cutaneous tuberculin samples (Mantu reactions) were sharply positive.

The non-sensitized animals received intravenous injections of ATK. We have included a curve from one of these experiments (Figure 5A).

In this experiment, 0.5 ml of physiological solution was injected intravenously and failed to produce any changes in the arterial pressure and respiration. The injection of 0.5 ml of ATK (1:10) caused a significant drop in arterial pressure, not accompanied by a significant change in the rate and depth of respiration. The pressure reached its initial level only /35

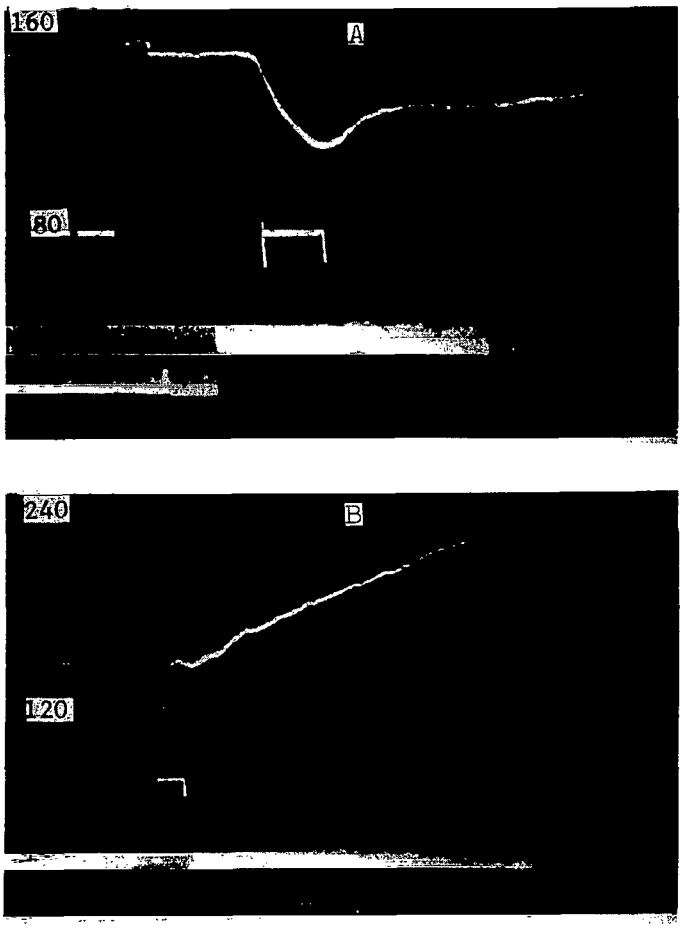

Figure 5. Change in arterial pressure and respiration in an intact rat with injection of ATK. A - Intravenous injection of tuberculin; B - Suboccipital injection of tuberculin. Curves from top to bottom: pressure in the carotid artery; stimulus mark; respiration; time mark (5 seconds). Ditto, zero pressure level.

10 minutes after injection of the tuberculin. The effect was similar in all other experiments in this series. The injections of small doses of ATK (0.5 or 1.0 ml ATK, 1:100) produced a brief, slight drop in arterial pressure. The pressure fell to a greater degree when the ATK dose was increased. Injection of undiluted tuberculin into the vein caused arterial pressure to drop to very low levels; this was followed by very slow recovery to the original level. Hence, all experiments of this group involving intravenous injection of tuberculin showed the same reaction: a drop in arterial pressure increasing with tuberculin dose.

The effect of ATK on the central nervous system was studied by injecting the preparation into the CSF of the animals (6 rats and 2 guinea pigs). For the sake of an example, we have included curves from one of these experiments (Figure 5B, a continuation of the preceding recording). In this experiment, 0.1 ml of ATK, 1:10 was injected into the CSF 11 minutes after the intravenous (i.v.) injection of ATK, when the arterial pressure had already returned to the original level. When the ATK was injected, there was a brief cessation of respiration and a drop in arterial pressure due to the reaction to the mechanical stimulus involved in injecting the substance. This effect rapidly

passed. The effect of ATK on the CNS is a prolonged increase in arterial pressure, i.e., a change opposite to that which occurs with i.v. injection of the same substance. The change in arterial pressure even in this case was not accompanied by a change in respiration. Injection of equal amounts of physiological solution into the CSF caused only a reaction to the actual process of injecting the substance into the spinal cord, without any subsequent changes.

The results of the other experiments were similar to the descriptions above. Direct action of ATK on the nerve centers always caused a prolonged increase in arterial pressure, i.e., a reaction opposite to that which developed in i.v. injection of the same substance. Hence, it appears that ATK is not a substance which is indifferent for the nervous system, at least for those branches of it which regulate the level of arterial pressure. It has a definite specific effect on the regulatory processes governing the latter. These results are analogous to the data of G. S. Kan (1954) and other authors and show that Koch's Old tuberculin is a stimulant for the nervous system.

However, it does not follow from these experiments that tuberculosis antigen is initially active. To study this problem, we used the same methodology to conduct experiments on animals which had been sensitized, i.e., with a high degree of sensitivity to the effect of tuberculosis antigen. /36

We injected ATK into the veins of 15 sensitized animals (12 rats and 3 guinea pigs). An example is shown in Figure 6A. Injection of tuberculin into the vein produced a drop in arterial pressure; the nature and degree of this reaction are the same as the reaction of the intact animals. Similar results were observed in all the other experiments of this series. Hence, /37 regardless of the fact that the sensitivity of the organism to the action of tuberculin increases to a tremendous extent with sensitization, the direct reaction of the cardiovascular system (drop in arterial pressure) to i.v. injection of ATK was the same as in the intact animals.

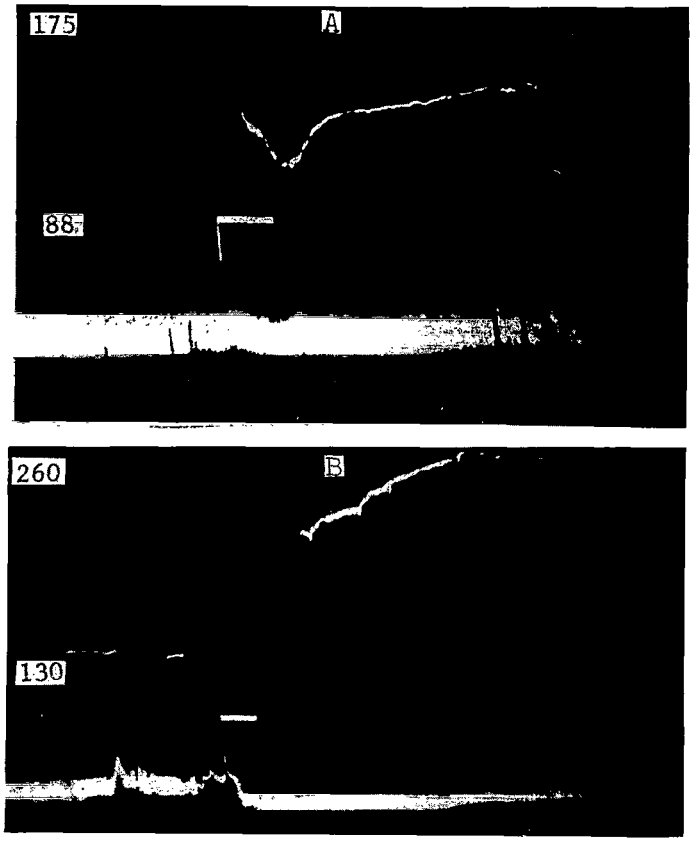

Figure 6. Change in arterial pressure and respiration in sensitized rat following injection of ATK. A - With intravenous injection of tuberculin; B - With sub-occipital injection of tuberculin. The markings are the same as in Figure 5. Due to movement of the animal, the curve for arterial pressure is broken.

To study the effect of ATK on the CNS of sensitized animals, we injected ATK into the CSF of 7 sensitized white rats and 2 guinea pigs. /38

Figure 6B shows the curve for one of these experiments. As we can see from the figure, the injection of tuberculin caused a sharp increase in arterial pressure which was not accompanied by significant changes in respiration. The reaction is the same as for intact animals. Similar results were observed in the other experiments in this group. ATK produced the same changes in sensitized and intact animals. We can therefore assume that the stimulation of the nervous system caused by the action of ATK which showed up in these experiments was not caused by the tuberculosis antigen itself, but by additional impurities present in ATK.

Let us emphasize once again that ATK is not a "pure" antigen. The technology for producing it is such that the finished product is a mixture of antigen and the decay products of a protein medium; the amount of these products is greater than the amount of the antigen substance itself. In this regard, F. A. Levtova (in the work mentioned previously) conducted control experiments to study the effect produced on the interoceptors by a "pure" medium, which is used in preparing tuberculin (bouillon), evaporated to the

same concentration as in the manufacture of tuberculin. She observed several differences in the action of the tuberculin and this "pure" medium, which were the result of a specific action on the nervous system exerted by the tuberculosis antigen. However, the differences which this author observed may depend on another factor, e.g., the fact that pure evaporated bouillon differs in composition from bouillon in which tuberculous bacteria have grown, for it is in the process of growth that the bacteria break down peptone and protein products. The action of the products of this breakdown differs sharply from the effect of unused evaporated bouillon. Hence, the results of the control experiments of F. A. Levtova appear to us to be insufficiently reliable.

We performed control experiments with an antigen purer than ATK, i.e., dry purified tuberculin (DT) prepared at the Leningrad Institute of Vaccines and Sera with the assistance of Prof. M. A. Linnikova (1939). The Mantu reaction, which appeared with both ATK and DT, indicated that the latter has pronounced antigen activity and gives positive tuberculin tests which do not differ in appearance from samples from tests with ATK. However, the content of nonspecific impurities in the DT, as we know, has been reduced to a minimum. Dry tuberculin was injected intravenously into 10 intact animals (7 rabbits and 3 guinea pigs). Figure 7A shows a recording from one of these experiments.

The injection of DT into the vein did not produce the characteristic drop in arterial pressure obtained with ATK, but evoked a reaction which differed slightly from that following injection of physiological solution. /39

Similar results were observed in all the experiments of this series. The arterial pressure did not change or increased very slightly (by 3 to 5%).

In experiments with 8 intact animals (6 rabbits and 2 guinea pigs), DT was injected into the CSF. Two examples from one of these experiments are shown in Figure 7B.

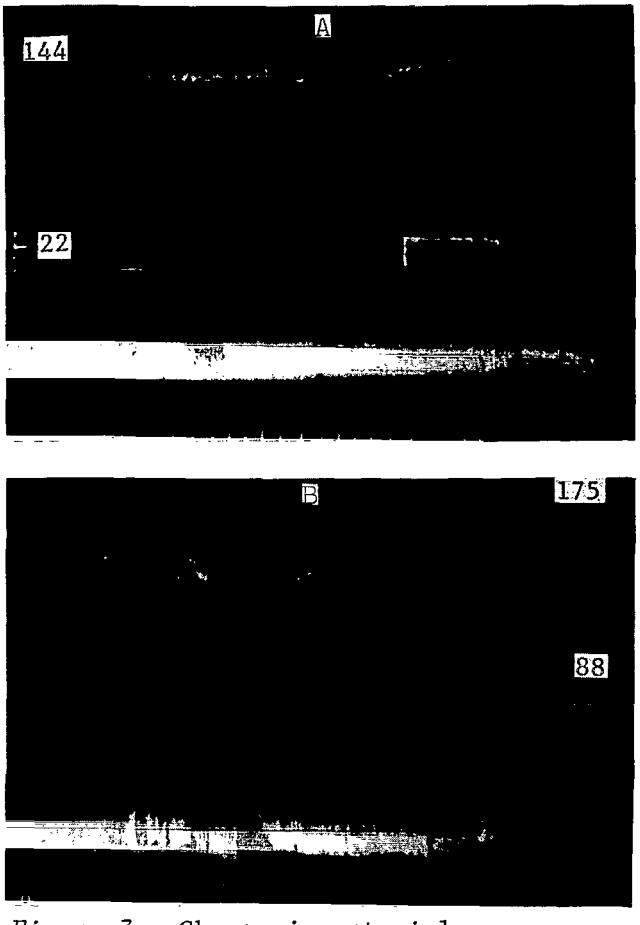

Figure 7. Change in arterial pressure and respiration in intact rat with injection of purified tuberculin. A - With i.v. injection. B - With suboccipital injection. Symbols same as Figure 5.

As the figure shows, aside from a brief reaction to the injection process itself, a solution of dry tuberculin coes not produce subsequent significant changes in arterial pressure and respiration.

In only three cases, injection of DT into the CSF was followed by /40 a very slight increase in arterial pressure; in six experiments, however, the pressure did not change.

None of the experiments in this series showed any contradictory reactions of the "center" and "periphery", indicating a specific action of the preparation on the nervous system.

The purpose of the next group of experiments was to investigate the action of DT (using the same method) on animals sensitized to tuberculin. DT was injected into the veins of the vaccinated animals (7 rats and 2 guinea pigs). Figure 8A shows a recording from one of these experiments. As we can see from the latter, the reaction of the experimental animal as far as its arterial pressure is concerned is the same as that of an intact animal: as in the latter, there is no drop in arterial pressure. Similar results were observed in all the experiments of this group.

The effect of dry tuberculin, when injected into the CSF of sensitized animals, was studied in four animals. A recording from one of these

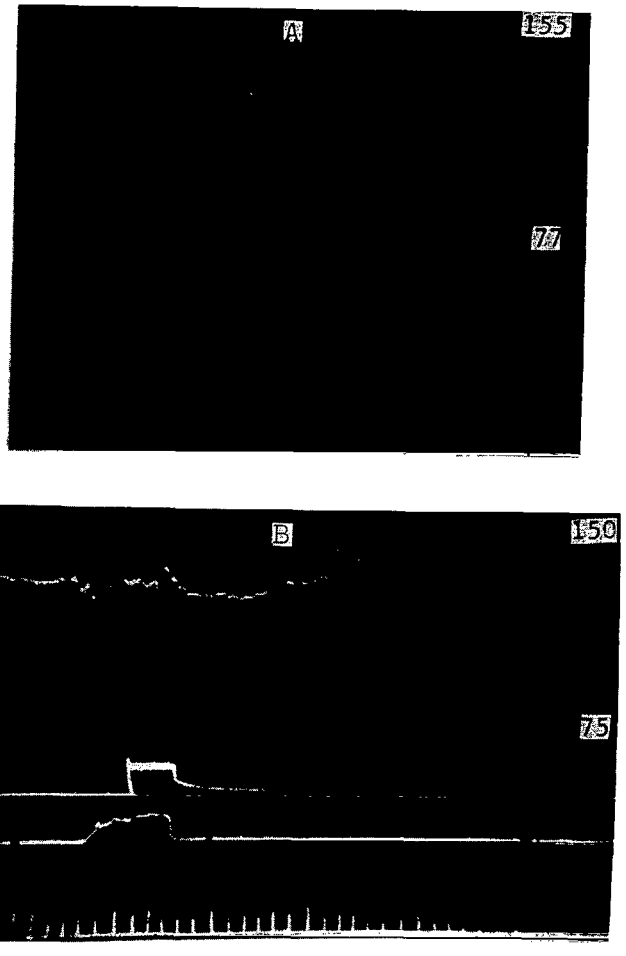

Figure 8. Change in arterial pressure and respiration in sensitized rat with injection of purified tuberculin. A - With i.v. injection; B - With suboccipital injection. Symbols the same as in Figure 5.

experiments is shown in Figure 8B. As we can see from the latter, the solution of DT produces only a slight increase in the arterial pressure. The reaction is the same as that in the intact animals. There is no contradictory reaction of the "center" and the "periphery" as is characteristic of ATK.

Thus, we can assume that the changes in the cardiovascular system which occur when ATK is injected are actually due to the influence of impurities in the ATK (products of the breakdown of the bouillon).

Similar data were obtained in our laboratory by A. I. Volegov (1965); in experiments using 304 guinea pigs, he studied the influence of ATK and purified tuberculin on the afferent impulses in the fibers of the vagus nerve. Intravenous injection of Koch's Old tuberculin (ATK) into intact animals caused a sharp increase in afferent impulses after 10 to 30 seconds; on the other hand, the injection of equal doses of different types of purified tuberculin (titrated back according to the activity in a cutaneous tuberculin reaction) failed to produce any changes in the bioelectric activity of the nerve. There were no changes in activity even when foreign native serum was injected.

In experiments with sensitized animals, both the latter and intact animals showed a sharp drop in the reaction to ATK and purified tuberculin for 10 to 30 seconds after injection. At later stages, however, (30 to 60 seconds), both substances produced an increase in impulses in the sensitized animals. However, this increase in later impulsation was also observed when foreign native serum was injected into sensitized guinea pigs.

Hence, it was found that the direct reaction which arises immediately after the injection of ATK is nonspecific and is related to the stimulant /41
effect of different "ballast" substances, which are in this preparation. The later reaction is a reaction to the antigen properties of the preparation. It appears only in sensitized animals and is triggered by the action of specific antigens.

Since activity in these cases develops only after several dozen seconds, we can assume that it does not develop as the result of a direct reaction of the receptors to the antigen, but as the result of stimulation of tissue receptors by substances which are liberated in the interaction between the antigens and the tissue. Hence, we were unable to support the viewpoint of /42
G. S. Kan regarding the fact that tuberculosis antigen is a specific stimulus for interoceptors. Tuberculin allergic reactions in no way resemble "specific reflexes" in their development. The specifics of the reaction depend on the effect of the antigen on the tissue and its mesenchymal elements. However, the intensity of the reaction is apparently determined to a significant degree by the regulatory effects of the nervous system.

Within the scope of the problems taken up in this book, it would be impossible to explain whether or not the development of tuberculin allergic reactions is affected by supplementary nonspecific stimulants.

This problem was studied by us (Kositskiy, Yashchenko, 1956) by producing Mantu reactions in guinea pigs suffering from tuberculosis.

Effect of Supplementary Nonspecific Stimulants on Tuberculin Allergic Reactions

In experiments using 22 guinea pigs, we studied the development of allergic reactions following infection of the animals with a virulent culture (Bovinus-8), with subcutaneous injection of tuberculin against a background of supplementary stimulation (subcutaneous injection in the other paw of 0.25 ml of turpentine). Eleven animals received the turpentine 35 to 90 minutes prior to the injection of tuberculin, while the others received it 35 to 90 minutes afterward. The results from the two groups of experiments were quite different. In those experiments in which the injection of the supplementary stimulant preceded the injection of tuberculin, there was an inhibition of the allergic reaction. However, when the injection of turpentine was given after the tuberculin injection, the tuberculin allergic reactions were sharply increased.

Hence, the combination of a supplementary nonspecific stimulus causes a change in the allergic tuberculin reaction. The most important aspect of this is that a comparatively small difference in the time of application of this supplementary dose of stimulant was found to be critical for the nature of a process which developed over dozens of hours. It seems to us that these phenomena demonstrate the principle of dominance. In particular, they show that the nature of the reaction depends on the order of action of the pathogenic and supplementary stimuli. The stimulus which is applied first is apparently the one which leads to the development of a focus of dominant excitation in the CNS; against this background, the reactions which arise under the influence of the second stimulus are inhibited.

However, the same supplementary nonspecific stimulus, used after the specific stimulus, accelerated development of the pathological process. This supports the more important significance of the time element, which has unfortunately been very little taken into account as yet in analyzing the mechanisms of the development of pathological processes. /43

We reached similar conclusions in our study of other pathological processes, especially air embolism, adrenalin pulmonary edema, anaphylactoid reactions, reactions to the injection of strophantin and reactions that involve sudden disruption of coronary circulation.

Air Embolism

The death of an organism from embolism arises out of a number of different causes. Along with the disruption of blood circulation to the vital organs, an important role is played by the development of pathological reflexes from the vascular reflexogenic zones.

The development of serious disturbances in the circulation and respiration during the first 10 seconds of a severe embolism and the resultant death of the organism involve the development of pathological reflexes, since it would be impossible in such a short space of time to develop metabolic changes which could shut off blood circulation.

This situation is explained by a number of phenomena which have been observed in the clinic and in the laboratory. We know, for example, that an organism can withstand without harm significant amounts of air injected slowly and gradually into the vascular tree; at the same time, however, a small air bubble (sometimes a small as 0.2 cm^3) which enters the vascular tree of a human being can lead to death. Sudden death from an embolism has even occurred in cases when only a small embolus, absolutely insufficient to cause purely mechanical disturbance of blood circulation in the lesser circulation, appeared in one branch of the pulmonary arterial tree.

A. I. Tal'yantsev (1911), A. B. Vogt and V. K. Lindeman (1901), Kozhin (1905) and N. G. Krol' (1941) in the laboratory of V. V. Parin, I. P. Davytaya (1952) and others were successful in demonstrating the important role of stimulation of vascular receptors in the lesser circulation in the development of pathological disturbances involving embolism.

In our experiments, we used this model of the pathological process to study the interaction of specific and supplementary (nonspecific) stimuli.

Course of Air Embolism Under the Influence of Supplementary Nonspecific Stimuli

In 10 control experiments, we injected 0.5 ml of air into the jugular vein of white rats weighing approximately 100 grams; this led to respiratory stoppage, spasms and death in 20 to 30 seconds. /44

In the experiments which followed, we inserted two platinum needles into the muscles of the right hip on both sides of the femur; through these needles, we applied faradic current from the secondary coil of a Dubois-Raymond apparatus (the voltage in the primary was 2 V). The current intensity was set so that the animals remained calm (the distance between the coils was 13 to 15 cm; for more detail on the method, see pages 66-67)*.

From 3 to 10 minutes (25 and 30 minutes in two out of the ten cases) after the current was switched on, against the background of its continuous action, we injected 0.5 ml of air into the jugular vein (the amount which caused death in the controls). Four of the ten rats died one to two minutes after injection of the air. The controls died 20 to 30 seconds later. The remaining six animals did not show the respiratory reactions and spasms that were typical of the controls. They remained alive during the days that followed.

In other experiments, the faradic current was switched on 10 to 20 seconds after the i.v. injection of air under the same conditions.

None of the 10 rats died 20 to 30 seconds after injection of air. One rat remained alive after injection of 0.3 ml of air, but it was removed from the stand in a state of shock (severe general collapse, reflexes sharply reduced, lying on its side). This state lasted several hours.

*Translator's note: This corresponds to English pages 82 - 85.

Hence, stimulation of the sciatic nerve and the hip muscles with faradic current, applied prior to injection of air into the vein, prevented death of the animals in the majority of cases, even when lethal doses of air were administered.

When the same supplementary nonspecific stimulus was applied after injection of the air into the vein, death followed. Consequently, in experimentally induced air embolism,as well as in the models described above, the outcome of the pathological process depended not only on the action of the stimulant itself, but also on the order of application of the specific and nonspecific stimuli.

We studied these phenomena in greater detail using the model of adrenalin edema of the lungs. Since our basic experimental studies were conducted on the model of adrenalin edema of the lungs, it is necessary to clarify the mechanism of the development of this pathological process in greater detail.

Adrenalin Pulmonary Edema

Pulmonary edema was first described by Laennec in 1819; this phenomenon consists primarily of the exudation of a serous fluid, rich in protein, into the alveoli (and to a lesser degree, the interstitial tissue of the lungs) in abundant quantities. As a result, respiration and gas exchange are disrupted, leading to asphyxia and death. /45

In pulmonary edema, the serous fluid passes directly through the wall of the pulmonary membrane which serves as a unique hematoparenchymatous barrier.

The hematoparenchymatous barrier (to use L. S. Shtern's terminology, histohematic barrier) is a combination of structural elements which are involved in the exchange of substances between the blood and tissues.

The modern views regarding the structure of the hematoparenchymatous barrier, as Zweifach (1957) points out, are combined in the following general picture: 1) a layer of adsorbed protein, covering the inner surface of the capillaries; 2) a purely endothelial membrane, consisting of cells and intercellular cementing substance; 3) a layer of intercellular cementing substance; 4) thin connecting fibers interwoven into a dense amorphous basic substance (pericapillary fibers); 5) a layer of connective tissue 25 to 50 microns thick between the capillaries and the cells.

Policard and Collet (1958) studying the structure of the capillary walls with an electron microscope, made some corrections in this concept. In their opinion, a continuous layer of closely packed endothelial cells develops from within the capillary and rests on the basal membrane; the reticulated fibers of the basal membrane are interwoven with the surrounding connective tissue; here and there are pericytes which enfold the capillaries with their branches, rest against the basal membrane or are located within the latter; the external layer of the hematoparenchymatous barrier is composed of pericapillary connective tissue.

Bargman (1955), working with an electron microscope, found that the cells of the capillary endothelium are capable of changing shape by becoming shorter and thicker. As a result, the permeability of the vessels may be reduced, since the author states (1958) that all the substances involved in the process of exchange between blood and tissue must pass through the endothelial cells. The important structural unit of the hematoparenchymatous barrier is felt by Berman to be the basal membrane; in his opinion, it is the principal factor on which the movement of molecules of different sizes depends.

Thus, as edema develops in any tissue, the fluid must overcome all the elements of the hematoparenchymatous barrier, whose structure has been quite thoroughly studied by Policard and Collet (1958), A. I. Smirna-Zamkova (1955) and Bargman (1958), etc.

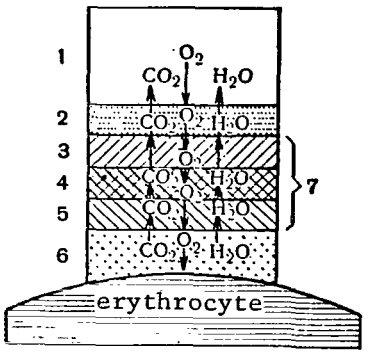

Figure 9. Diagram of the structure of the pulmonary membrane (according to Macklin, 1954). 1 - Alveolar air; 2 - Mucous membrane (0.2 microns); 3 - Respiratory epithelium (0.2 microns); 4 - Connective tissue (0.2 microns); 5 - Endothelium of pulmonary capillaries (0.2 microns); 6 - Plasma; 7 - Air-blood protoplasmic barrier, 0.6 microns, visible in electron photomicrographs.

The Pulmonary Membrane

In the development of pulmonary edema, the fluid which passes into the alveoli must also pass through a special hematoparenchymatous barrier (the pulmonary membrane). The latter consists of the tissues which bound the alveolus and the capillary walls /46 in close proximity to it. Modern concepts regarding the pulmonary membrane are based on the results of both optical and electron microscopy.

This problem was studied by Hayek (1953), Bargman (1955, 1958), Macklin (1955), Wolf (1953), Groodt, et al. (1955) and other authors. According to their data, the structural elements of the pulmonary membrane are as follows: the capillary endothelium and alveolar epithelium, which are in contact with the basal membrane itself, and a narrow space between the two basal membranes, filled with a thin layer of connective tissue with elastic reticular fibers. The pulmonary membrane is very thin, varying in thickness from 0.3 to 0.6 microns (Figure 9).

One of the particular features of the structure of the pulmonary capillaries is the absence of pericytes in their walls. The permeability of the pulmonary membrane depends on the configuration of the elongated cells of the capillary endothelium itself and the flat cells of the alveolar epithelium. When these cells grow short and thick, the pulmonary membrane grows thicker and its permeability may decrease. However, when the membrane cells contract excessively, permeability may increase due to exposure of the basal membrane,

since the latter readily allows liquid to pass from the capillaries into the alveoli (Hayek, 1953; Bargman, 1958).

Pathogenesis of Pulmonary Edema

As of the present time, there is no single generally accepted concept of the pathogenesis of pulmonary edema. Among Soviet investigators, the most work in this field has been done by Ya. A. Lazaris and I. A. Serebrovskaya (1962). From our standpoint, they are successful in generalizing the most important factors determining the development of pulmonary edema. These /47
consist primarily of hemodynamic disturbances which lead to an increase in the hydrostatic pressure in the capillaries. Also involved are the state of permeability of the pulmonary membrane, the hydrophilia of the tissue, the state of the lymph circulation, the level of the oncotic pressure of the blood plasma, etc.

Pathoanatomists differentiate between congestive, toxic and neurotic pulmonary edema. The development of the latter involves different pathological states and damage to the CNS. In the majority of cases, the development of pulmonary edema involves all of these factors; however, the degree of participation of each of them in each individual case may differ. In the following, we shall discuss the principal causes of the development of pulmonary edema: hemodynamic disturbances, changes in permeability of the pulmonary membrane, and various injuries to the nervous system.

Disruption of Hemodynamics

The majority of hemodynamic disturbances, accompanying the development of pulmonary edema, may be divided into two main groups: a) mechanical inhibition of blood flow from the pulmonary vessels; b) an increase in the influx of blood into the lesser circulation.

The first experimental studies that were devoted to determining the nature of the mechanism of the development of pulmonary edema were conducted

by Welch in 1878, a fellow worker of Konheim. Welch showed that ligation of the aorta and its large branches (in the rabbit, more rarely in the dog), constituting a severe overload on the left heart, can produce pulmonary edema with normal function of the right ventricle. The left ventricle cannot pump blood from the lesser circulation into the greater circulation, leading to stagnation of the blood in the lesser circulation and an increase of pressure in the latter. As a result of stagnation of the blood and an increase in the hydrostatic pressure in the pulmonary vessels, blood plasma passes from the capillaries into the alveoli.

Welch was also successful in obtaining pulmonary edema by ligating several pulmonary veins, naturally leading to blood stagnation in the pulmonary tree. We must point out that Welch performed his experiments under the conditions of an open chest cavity and artificial respiration, when there is significant disruption of hemodynamics and pulmonary edema develops mainly in the agonal state of the animal.

It should also be pointed out that mechanical sensors of disruption of hemodynamics do lead to the development of pulmonary edema in the majority of cases, but their number is small. In connection with all of the above, the "mechanical" theory of the origin of pulmonary edema suggested by Konheim and Welch encountered opposition as soon as it was suggested. Moreover, Sahli (1885) did not confirm Welch's data; in his experiments, ligation of the aorta did not produce development of pulmonary edema. /48

In the opinion of the authors, and those who adhere to the "mechanical" theory, the critical factor in the development of pulmonary edema is the change in the value of the filtration pressure, which depends in turn on the relationship of the values of hydrostatic pressure in the pulmonary capillary blood (5-10 mm Hg) and the oncotic pressure of the blood plasma (25-30 mm Hg) blocking it.

However, the experimental data of Paine, et al.(1949, 1950, 1952), who conducted experiments using Welch's method of ligation of the aorta and the

large vessels, showed that there is no strict relationship between the capillary pressure in the lungs and the intensity of the development of pulmonary edema. According to the data of these authors, edema developed in all the experimental animals only at a pulmonary capillary pressure in excess of 50 mm Hg.

Tissier, et al.(1901), ligated the aorta in curarized dogs, using artificial respiration; the pulmonary arterial pressure increased 2 to 3 fold as a result. However, pulmonary edema did not develop.

According to the "mechanical" theory of Welch, the development of pulmonary edema requires satisfactory working of the right ventricle with insufficiency of the left. This position was checked by Cataldi (1935). He produced different damage to the two ventricles of the heart by injecting silver nitrate and found that when the right ventricle was damaged, edema developed in 2/3 of the cases, while when the left ventricle was damaged pulmonary edema occurred in only rare cases. Similar observations made by Bettelheim (1892) agree with these findings.

We know from clinical practice that severe pulmonary edema can sometimes be arrested without therapeutic intervention. If the development of edema were dependent solely on mechanical conditions, then obviously such phenomena would not be observed (Umanskiy, 1937).

Wasserman, et al. 1946 agree with this point of view; they feel that the clinical cases of paroxysmal pulmonary edema cannot be explained merely by severe left ventricular insufficiency. Wasserman pointed out that the spasms of cardiac asthma in patients who have developed pulmonary edema are accompanied not by a drop in arterial pressure, as we would expect in the case of severe left ventricular insufficiency, but by an increase in it. The author views this as the consequence of a strong stimulus of the sympathetic nervous system in asthma, indicated (in his opinion) by tachycardia, increased sweat production, and a rise in arterial pressure. On the basis of the fact that pressing with the finger on the region of the carotid sinus often stops

an attack of cardiac asthma and prevents the development of pulmonary edema, he suggests that a reduction of the tonus of the sympathetic nervous system is involved, along with a rise in the tonus of the parasympathetic nervous system. /49

Wasserman gives a unique point of view regarding the possible mechanisms of the development of pulmonary edema in cardiac pathology. The sharp variations in arterial pressure that develop in heart disease, which stimulate the receptor apparatus of the sino-carotid zone to varying degrees, finally lead to a severe increase in arterial pressure in the greater circulation. This causes an overload on the left ventricle and then overfilling of the lesser circulation; the latter results in a rise in the permeability of the pulmonary capillaries.

The data of Wasserman agree with the observations of S. I. Umanskiy (1937) and Yu. I. Lorie et al. (1947). If we use the mechanical theory as a basis, we cannot explain the fact that pulmonary edema develops markedly in mitral stenosis, which as we know causes very severe blood stagnation in the lungs as a result of disruption of blood flow out of the lesser circulation.

It is obvious from all of the above that the so-called mechanical theory of the origin of pulmonary edema has some important shortcomings, which do not satisfy clinicists and are not supported by all experimenters.

A number of authors feel that an important role in the development of pulmonary edema is played by redistribution of the blood from the greater circulation to the lesser, which occurs under certain conditions. Thus, for example, Marinescu and Ionescu (1956) observed rapidly developing pulmonary edema in patients with mitral stenosis and negative emotions. Luisada and Cardi (1955), on the basis of their experimental findings, feel that negative emotions increase the tonus of the vasoconstrictors so that the blood is redistributed from the greater circulation to the lesser.

The most reliable experimental basis for this idea was provided by Sarnoff et al.(1952a, b, 1953). He feels that stimulation of the CNS, leading to redistribution of the blood from the greater circulation to the lesser may not be a consequence of emotional stimulus alone. It may be caused by a reflex mechanism involving the receptors of the carotid sinuses, and may develop with direct stimulus of the CNS. He reached this conclusion on the basis of experimental results in which animals were given a coagulant mixture of fibrinogen as a stimulant, together with thrombin, through the atloidooccipital membrane into the subarachnoid space (into the cisterna magna). The intracisternal injection of this mixture in rabbits and dogs was accompanied by the development of fatal pulmonary edema in practically all cases, and the author explained the mechanism as follows: direct stimu- /50
lation of the vasomotor center leads to a pronounced stimulation of the nervous system, causing a sharp constriction of the vessels in the greater circulation and a marked drop (expression) of blood into the veins, an increase of blood flow into the right heart and consequent overfilling of the pulmonary vessels. Constriction of the peripheral vessels causes a sharp increase in the arterial pressure in the greater circulation, leading to an increase in the load on the left ventricle, which under these conditions is not in a position to shunt into the arteries all of the blood which is coming from the pulmonary vessels. This leads to blood stagnation in the lesser circulation, an increase in the hydrostatic pressure (and therefore in the filtration pressure) in the latter, leading to development of pulmonary edema. These results are based on the fact that immediately after intracisternal injection of the fibrin mixture there was an increase in arterial and venous pressure in both the lesser and greater circulations. The pulmonary venous pressure in dogs rose to 75 mm Hg, and the amount of blood flowing through the aorta dropped sharply; the left auricle enlarged 4 to 5 times, and the pulmonary veins also distended.

Similar hemodynamic disturbances in the development of pulmonary edema were observed in intracisternal injection of other stimulants; turpentine — 0.03 to 0.05 ml (Chernukh, 1950, 1952, 1954); chloramine (Speranskiy, 1942);

air or veratrine (Aravanos, 1957), and with strictly localized stimulation of the hypothalamus by electric currents (Maire, Patton, 1954).

Ya. A. Lazaris and I. A. Serebrovskaya (1962) feel that this mechanism for the development of pulmonary edema may occur in cardiac patients, especially with mitral stenosis, in the stage when blood flow from the lungs has already been disrupted and impeded. Emotional disturbances under such conditions, causing sympathetic vasoconstriction, may lead to "redistribution of the blood" from the greater circulation to the lesser.

Wasserman also mentions a similar mechanism for the development of pulmonary edema. In his opinion, the reflexes from the carotid sinus (when there is insufficient blood flow to it from the left ventricle) and the consequences of the drop in arterial pressure may normally culminate in sympathetic vasoconstriction as the organism attempts to raise the pressure through the autoregulatory mechanism, leading to redistribution of the blood from the greater circulation to the lesser.

In all of these cases the development of pulmonary edema has theoretically the same result: an increase in the blood volume in the lesser circulation due to increased filtration pressure, leading to development of pulmonary edema.

However, a significant rise in pressure in the lesser circulation is not always accompanied by development of pulmonary edema. Pulmonary edema may arise in animals and man against a background of general marked hypotonia and a drop in pressure in the lesser circulation (for example, in traumatic shock) (Moon and Kennedy, 1932). /51

Loewit (1893) says that pulmonary edema which develops with prolonged artificial respiration may also occur against a background of reduced pressure in the lesser circulation, the left ventricle and the carotid arteries. V. S. Savel'yev (1958) also observed pulmonary edema in patients with mild and medium degrees of pulmonary arterial hypotonia (40-70 mm Hg), with an arterial pressure usually less than 30 mm Hg, more frequently than at higher

pressures. The observations of Aravanos, et al. (1957) do not agree with the theory of "redistribution" of Sarnoff; they showed that subarachnoidal injection of air or irritation of the hypothalamus results in development of pulmonary edema even when the greater circulation is disconnected.

One form of hemodynamic edema is experimental adrenalin pulmonary edema (Luisada, 1928; Kan, 1953 et al.). The intravenous injection of toxic doses of adrenalin in experimental animals leads to rapid development of pulmonary edema, accompanied by marked hemodynamic disturbances similar to those described by Sarnoff (1952, 1953) in the intracisternal injection of fibrinogen with thrombin. However, even when adrenalin was injected into the blood, pulmonary edema did not always develop. Thus, G. S. Kan showed that in contrast to intravenous injection, intra-arterial injection of adrenalin (although it does produce the usual hemodynamic changes) does not cause development of pulmonary edema. Kan states that in addition to an increase in hydrostatic pressure and redistribution of the blood, there must also be a disruption of the permeability of the membrane.

Hence, neither the "mechanical" theory of Welch and Konheim, nor the theory of "redistribution" of the blood, can completely explain the mechanism of development of pulmonary edema. In this regard, a number of authors suggest that it is impossible to explain the pathogenesis of pulmonary edema as a whole on the basis of individual disturbances of hemodynamics. There is sufficient basis for feeling that the disruption of the permeability of the pulmonary membrane is very important in this respect.

Change in the Permeability of the Pulmonary Membrane

The development of pulmonary edema with general vascular hypotonia, its prevention against a background of high pressure in the lungs and independence of the beginning of development of pulmonary edema on the level of pressure in the lesser circulation: all of these justify a search for other reasons to explain the origin of pulmonary edema. It is natural for us to think

first of all of the important role of the change in permeability of the pulmonary vessels during the development of edema.

According to the theory of Konheim and Lichtheim (1877), an important role in the development of pulmonary edema is played by the change in the functional state of the endothelium of the pulmonary capillaries. The authors feel that either a chemically active substance in the blood or lymph or a drop in the oxygen of the blood might cause a change in the permeability of the endothelium of the capillries. However, the authors did not provide any direct evidence of changes of membrane permeability. /52

The majority of articles which mention changes in permeability of pulmonary vessels, accompanied by the development of edema, are based on indirect data, although the possibility of increasing the permeability of the vascular capillaries in the development of pulmonary edema is not disputed as a rule.

The toxic and hypoxic theory of Konheim and Lichtheim has not been proven even at the present time. The hypoxic theory of the origin of pulmonary edema contradicts the fact that gas exchange in the lungs takes place rapidly so that the tissue of the lungs is provided with sufficient oxygen even with significant hemodynamic disturbances. There are also reliable indications of the absence of any change in permeability of the vessels in hypoxia. Thus, Rech (1963), showed in his experiments with guinea pigs that the permeability of the mesothelium is not disturbed when the animals are kept in a gas mixture consisting of 4% oxygen and 96% nitrogen, although some animals died of anoxia under these conditions.

We might suggest that hypoxia is accompanied by the formation of non-oxidized products which have a toxic effect on the pulmonary membrane. However, thus far, no endogenic toxic substances have been found which are formed in hypoxia and which increase the permeability of the pulmonary vessels. At the same time, considerable data have been accumulated which indicate that the pulmonary membrane is irritated by the action of exogenic toxic substances.

Laker, et al.(1932) and N. A. Soshestvenskiy (1933) showed that edema of isolated lungs develops about an hour after cats have been poisoned with phosgene at a perfusion blood pressure of 30 to 40 mm Hg, and at 82 mm Hg in animals that have not been poisoned, which is an indication of an increase in the permeability of the vessels under the influence of phosgene. The same thing is indicated by the high content of protein in the edematous fluid in phosgenic and diphosgenic edema of the lungs (Cameron and Courtice, 1946). The amount of protein in the edematous fluid was felt by Ya. A. Lazaris and I. A. Serebrovskaya (1962) to be one of the principal indicators of an increase in the permeability of the pulmonary membrane.

It is important to keep in mind that with certain effects on the nervous system even direct irritation of the pulmonary membrane is not accompanied by an increase in permeability. Thus, Laker et al. prevented phosgenic and diphosgenic pulmonary edema by preliminary vagotomy in the neck, G. S. Kan (1953) by a vagosympathetic block. A. K. Sangaylo, et al.(1935), who produced edema in certain portions of the lungs by the action of nitrous oxide, observed hyperemia in symmetrical areas in the other lung. This form of edema develops against the background of low pressure in the greater and lesser circulations. It is natural that under these conditions it might arise only as a consequence of the disruption of the permeability of the pulmonary membrane. Development of this pulmonary edema was inhibited by substances (chloral hydrate, aminazine, sympatholytin) which change the functional state of the nervous system (Serebrovskaya, 1958).

Luisada and Sarnoff (1946a, b, c) feel that when a physiological solution /53 is injected into the carotid artery the permeability of the pulmonary vessels may change in a reflex response due to stimulation of the baroreceptors of the carotid sinus, the pulmonary vessels, and the heart. G. S. Kan (1953) has a similar opinion.

Direct indications of an increase in permeability of the pulmonary membrane in pulmonary edema were obtained by Meessen and Schulz (1957) using electron microscopy. They produced edema by intraperitoneal injection of

alpha-naphthylthiourea, cyosemicarbazide (a derivative of thiourea) or by ligation of the pulmonary vein which runs from one of the lobes of the lung. The authors observed a number of stages of development of pulmonary edema. At first there was an intra-epithelial edema (swelling of the processes of the epithelial cells). The epithelial cells lost contact with one another and exposed portions of the capillaries were seen, which sometimes led into the lumina of the alveoli. With further swelling of the epithelial cells, the basal membrane ruptured and interalveolar edema developed. The experimenters also observed rupture of the capillary endothelium of the capillaries. In the final analysis, the overall thickness of the pulmonary membrane increased from 0.6 to 2.5 microns. The morphological changes in pulmonary edema from different causes were the same.

Hence, at the present time there are both indirect and direct indications of the disruption of the permeability of the pulmonary membrane in the development of pulmonary edema.

It should be emphasized that many factors point to an important role for the nervous system in the change in permeability of the pulmonary membrane. As we have already mentioned, this is indicated even in those cases when the toxic substances (phosgene, for example) act directly on the alveolar epithelium (Laker, 1932; Tonkikh, 1949). In view of the fact that this problem is very important for our work, we must consider it in more detail.

Role of the Nervous System in the Development of Pulmonary Edema

Innervation of the lungs. The afferent fibers from the lungs are included in the vagus, upper laryngeal, phrenic and spinal sensory nerves (Lashkov, 1963; Kupriyanov, 1959; Grigor'yeva, 1954; Zabusov, 1941; Aviado, Schmidt, 1957, et al.). In all layers of the pulmonary arteries and veins, there are many sensory endings of chemo- and mechanoreceptor type. The pulmonary veins are significantly richer in arteries with mechanoreceptors.

The efferent innervation of the lungs takes place via the sympathetic /54
and parasympathetic nerves. The sympathetic fibers which serve the pulmonary veins originate in the cells of the lateral crescent of grey matter in the third through seventh thoracic segments of the spinal cord.

The fibers to the lungs run from the stellate and cervical sympathetic nodes; the parasympathetic nerves of the pulmonary vessels, in the opinion of the majority of investigators, are vasodilators.

Shternberg and Tamari (1928) are of the opinion that the centers which regulate alveolar blood circulation are located in the diencephalon and the mesencephalon (more exactly, in the vicinity of the medulla oblongata). An indirect basis for this concept is the results of experiments with intravenous injection of India ink, causing contraction of the small vessels of the lungs. Deep anesthesia prevents this narrowing of the vessels, but removal of the hemispheres does not affect this reaction; decerebration (with retention of the mesencaphalon and diencephalon) sharply reduces it.

Effect of Vagotomy on the Development of Pulmonary Edema

Many investigations have shown that bilateral vagotomy alone as a rule leads to the development of inflammation, "vagus pneumonia" and pulmonary edema, and can also cause a marked change in the course of pulmonary edema caused by other factors. A great many experimental studies have been devoted to the nature of these phenomena. However, both the actual data and the conclusions from them contain many contradictions.

As early as 1847, Schiff formulated the "neuroparalytic" theory of the development of pulmonary edema on the basis of the assumption that the vagus nerves are vasoconstrictors for the lungs and that cutting them produces neuroparalytic hyperemia. This causes the lungs to develop stagnation phenomena which increase transudation of fluid from the alveolar vessels. However, there are many data at the present time which show that impulses

can be transmitted along the vagus nerves that cause the pulmonary vessels to dilate rather than constrict. Thus, Shepherd et al.(1959) and Marshal, et al.(1959) found that stimulation of the cholinoreactive system of the pulmonary vessels by very small doses of acetylcholine (by injecting it into the lesser circulation) relieves the spasms of the pulmonary arterioles. These data provide us with a basis for stating that pulmonary vasodilators are of a parasympathetic nature and consequently belong to the vagus nerves.

The second widely accepted theory of the development of "vagus pneumonia" is the aspiration theory, linked with the views of Traube (1871). According to this theory, the changes in the lungs are related to many extrapulmonary factors that develop following vagotomy; laryngospasm, inspiration of food, loss of sensitivity of the mucous envelopes of the bronchi, disappearance of the Hering-Breuer reflex and disturbances in heart action.

This theory has also encountered a number of objections. Thus, F. Alex- /55
androv (1892) howed that paralysis of the rima glottidis and deglutition have no role whatsoever in the formation of pulmonary edema, since cutting of the accessory and recurrent nerves does not produce edema. Constriction of the rima glottidis also does not cause pulmonary edema by itself.

In his experiments, Farber (1937a, b, 1940) observed changes in the lungs similar to those which develop when the vagus nerves are cut. These changes appeared when the radix of the lung was covered with a cloth moistened in 1% novocain, thus causing temporary denervation of the lungs. In other experiments, the author prevented laryngospasms and aspiration, but vagotomy under these conditions gave a similar result. Reichsman (1946) also showed that prevention of laryngospasm by a low vagotomy does not prevent development of pulmonary edema, which usually arises following this operation.

Hence, the neuroparalytic theory of Schiff and the aspiration theory of Traube encounter a number of contradictions. Now, it is not surprising that the vagus nerves are carriers of afferent impulses from the pulmonary vessels. It has been shown that when the pressure in the lesser circulation changes,

the pressure in the vessels of the greater circulation changes in the opposite direction. The vagus nerves form the afferent branch of this reflex (Parin, 1946; Aviado and Schmidt, 1955, et al.).

The role of the afferent fibers of these nerves in the development of pulmonary edema has been studied in particular in various experimental models. Thus, Kraus (1913) showed that the afferent impulses from the lungs, passing into the CNS via the vagus nerves, participate in the realization of the discharge reaction of the lesser circulation preventing development of pulmonary edema in plethora. The disruption of this reflex arc leads to rapid development of pulmonary edema in plethora.

Kraus' data were supported by Farber (1940), but the author felt that the cause of the development of edema following vagotomy was the exclusion of efferent impulses from the lungs. Later on, however, many investigators have experimentally determined the important role of afferent impulses from the lungs in the development of pulmonary edema. Thus, A. V. Tonkikh (1949) observed that the electrical or mechanical stimulation of the afferent fibers of the vagus nerve produces pulmonary edema or pneumonia. A. M. Chernukh (1954), stimulating the central ending of the right vagus nerve in the neck of the rabbit by injecting into it 0.03 to 0.05 ml of turpentine, observed /56 development of pneumonia or pulmonary edema in all cases.

The observations of G. S. Kan (1953) agree with the data of A. M. Chernukh and A. V. Tonkikh. In his experiments, a subthreshold dose of adrenalin failed to produce pulmonary edema in control rabbits. However, when the same injection of adrenalin was accompanied by stimulation of the central ending of the vagus nerve, fatal pulmonary edema developed.

The concept that impulses which allow development of pulmonary edema pass along the vagus nerves has been employed by various investigators in the prophylaxis of edema by excising these nerves in the experiment. Thus, the inhibitory effect of vagotomy on the development of edema was observed by K. Laker et al.(1932) in their study of toxic edema produced by phosgene.

Cutting of both vagus nerves in the neck into two stages prevented the development of edema in 12 out of 22 cats. However, when S. I. Yenikeyev (1944) performed the same experiments, he was unable to prevent the development of phosgenic pulmonary edema. K. M. Bykov et al. (1943a, b) prevented the development of adrenalin edema by bilateral vagotomy. However, in the experiments of Cassen and Kistler (1954a, b) vagotomy not only did not inhibit the development of pulmonary edema, but even accelerated it. There are scattered indications (Weiser, 1923; Rabinovich, 1940) that vagotomy increases the permeability of the pulmonary vessels. In addition, the experiments described above in which vagotomy produced development of pulmonary edema also contradict these concepts.

The data presented above indicate the complex nature of the effect of the vagus nerves on the development of the pulmonary edema. Apparently, this also explains the contradictory nature of the data which are obtained under different conditions by different authors.

The Effect of the Sympathetic Nerves on the Development of Pulmonary Edema

The sympathetic nerves, in a widely held opinion, are vasoconstrictors. "Unfortunately, there are almost no indications of the sympathetic vasoconstriction of the venous portion of the lesser circulation. At the same time, however, it is understandable that spasms of the venous vessels could serve as a hemodynamic explanation for pulmonary edema with an increase in the flow of sympathetic impulses to the lungs. Spasms of the arterioles, on the other hand, act as a mechanism that weakens capillary hypertonia in the lesser circulation," emphasize A. Ya. Lazaris and I. A. Serebrovskaya (1962).

Desympathization of the lungs may considerably reduce the development of edema, caused by different methods. Thus, Boggian (1929) prevented adrenalin pulmonary edema by uni- and bilateral extirpation of the stellate nodes; Luisada (1928) achieved the same effect by cutting the spinal cord between the middle cervical segments. According to the data of E. P. Rudin

(1963), removal of the stellate nodes ten to twenty days before the experiment prevented the development of edema in the majority of cases involving i.v. injection of 10% chloramine. Only 8 out of 34 experimental dogs died of pulmonary edema, while all the animals perished in the control series of experiments. /57

By removing the upper cervical sympathetic node, A. V. Tonkikh was able to prevent the appearance of diphosgenic pulmonary edema, which it is felt develops as the result of irritation of the pulmonary membrane and an increase in its permeability.

Together with data which indicate an inhibitory effect of desympathization of the lungs on the development of edema, opposite results have also been described.

Thus, Ferguson and Berkas (1957) produced pulmonary edema by means of a sharp increase in the hydrostatic pressure in the pulmonary vessels by diverting the blood through a shunt from the bronchial artery to the pulmonary artery. Using this model, the authors found the denervation of certain segments of the lungs speeded up the development of edema at a lower pressure in the same denervated segment. The authors feel that with an excess flow of blood into the arteries in the lesser circulation, the development of edema in those segments of the lungs in which the innervation is intact prevents the spasms of the precapillary vessels which develop as the result of the influence of the sympathetic nerves.

The involvement of the sympathetic nervous system in the pathogenesis of pulmonary edema is accomplished not only by the changes in the hemodynamics in the lesser circulation, but also by the influence on the vascular permeability. This was shown in the experiments of Nissel (1950). He produced edema of an isolated lung that was perfused for a long time with a blood substitute. When perfusion was accompanied by stimulation of the nerve fibers running from the stellate node, edema developed twice as rapidly (at the same perfusion in both groups of experiments). The author suggests that pulmonary edema

develops more rapidly under these conditions as the result of increased permeability of the capillaries.

The understanding of the true role of the sympathetic nervous system in the development of pulmonary edema is complicated by the fact that an increase in tone, which leads to a constriction of the precapillary vessels, prevents the development of edema, while stimulation of the sympathetic nerves may increase the permeability of the vessels and facilitate the development of edema.

The Effect of Stimulation and Excision of Certain Segments of the Central Nervous System Upon the Development of Pulmonary Edema

Pulmonary edema is a frequent complication of problems affecting the nervous system (Levantovskiy, 1939; Luisada and Cardi, 1956), often leading to the death of the patient. Under experimental conditions, edema often arises with damage or trauma affecting the head.

Thus, Cassen and Kistler (1954a) produced pulmonary edema in mice by an /58
explosion wave. Protecting the heads of the experimental animals against the air shock by a shield sharply reduced the intensity of the edema which developed. The same protection applied to the chest cavity (rib cage) had no effect on the development of edema. The authors felt that cholinergic substances (carboxylin, mecholin, pilocarpine) prevented edema in trauma to the head, while bilateral vagotomy intensified it.

Pulmonary edema may be produced by injection of different stimulants into the subarachnoid space: coal tar, coagulant mixtures of fibrinogen and thrombin, turpentine). All of these stimulants produce similar reactions as far as the lungs are concerned: initial hyperemia, hemorrhagic edema, and pneumonia after 16 to 22 days. This picture develops against a background of progressive hypertonia of the lesser circulation due to constriction of

the pulmonary vessels and redistribution of the blood (Maire and Patton, 1954, 1956a, b; Sarnoff, 1952).

However, with a similar subarachnoid injection of 0.03 to 0.05 ml of turpentine in rabbits, A. M. Chernukh (1950, 1952, 1954) also observed pronounced hyperemia and insignificant pulmonary edema, with pneumonia at later stages. Unilateral vagotomy, like stimulation of the vagus nerve, in his experiments intensified the development of edema on the same side.

Maire and Patton produced pulmonary edema in rats by strictly localized stimulation of the pre-optical zone of the hypothalamus with an electric current of 4 microamperes for 21 to 32 seconds, using a unipolar electrode. The authors feel that the electric current in this case excludes certain pathways passing directly above the optic chiasm and even created the impression that there is an "edemogenic center" located somewhat behind the preoptic zone, whose disturbance (or the disturbance of its descending pathways) excludes the possibility of developing pulmonary edema in case of damage to the preoptic region. According to the data of the authors, vagotomy does not (but cutting of the spinal cord does) prevent the development of pulmonary edema. They feel that pulmonary edema involving stimulation of the hypothalamus develops as the result of a shift of blood from the abdominal cavity to the lungs, caused by a sharp constriction of the vessels in the abdominal organs, since cutting of the splanchnic nerves prevents this "preoptic" pulmonary edema. This is supported by the fact that, when the splanchnic nerves are cut, the weight of the liver and spleen does not decrease. As we know, this is observed when intact splanchnic nerves are stimulated as the result of expression of blood from them (and, consequently, from the organs in the abdominal cavity) and overfilling of the lesser circulation.

Cameron and De (1949) produced pulmonary edema by the intracisternal injection of a coagulant fibrin mixture, in which the development of edema was inhibited following preliminary bilateral vagotomy, atropinization and cocainization. Vagotomy alone was unable to affect the hemodynamic changes

accompanying the injection of these mixes. However, cutting of the vagus nerves in similar experiments by Sarnoff et al. (1952a, b, 1953) did not lead to the development of edema. /59

These data indicate that exclusion of the peripheral nervous system may have an influence on the course of pulmonary edema of central origin.

Several investigators have suggested that exclusion of the central nervous system may inhibit the development of pulmonary edema. Thus, according to the data of A. G. Kravchenko (1959a), decerebration between the lamina quadrigemina or at the level of the posterior lamina quadrigemina in cats prevented the development of adrenalin edema in 9 out of 13 cases. The author feels that the pathological reflex which leads to the development of pulmonary edema may be incorporated in the brain stem at the level of the lamina quadrigemina or beneath it.

Hence, the participation of the nerve apparatus in the development of pulmonary edema is quite clearly evident. Contradiction of experimental data on the effect of the nervous system on the development of pulmonary edema obviously is explained primarily by the complexity and the diversity of forms of its participation in the development of this pathological process. Only a tedious accumulation of the very newest data will make possible a more detailed study of the pathogenesis of this complex syndrome.

Features of Adrenalin Pulmonary Edema

One of the most reliable ways to obtain pulmonary edema is intravenous injection of adrenalin. The initial effects of the extract of the adrenal glands on the organism of several animals (rabbits and guinea pigs) began to be studied in 1894 by the Russian scientists Tsybul'skiy and Simanovich and the Englishmen Oliver and Sheffer, working independently. These investigators observed the development of fatal pulmonary edema which developed when patients were injected with a dose of preparation. However, as the model for obtaining pulmonary edema, this experimental method was worked out much later

by Luisada (1928), Shternberg and Tamari (1928) and Glass (1928). They also showed the significance of nerve mechanisms in the genesis of this edema.

We must take into account the fact that the adrenalin model of pulmonary edema is hemodynamic. At the present time, the disruption of hemodynamics arising after injection of adrenalin into the greater and lesser circulations and leading to the development of edema has been sufficiently well studied. It is accompanied by spasms of the peripheral vessels and a sharp increase in the arterial pressure in the greater circulation so that the blood, so to speak, is expressed from the internal organs into the venous tree. This /60 causes an increase in the influx of blood into the right heart and accordingly into the pulmonary vessels. With a sufficiently high arterial pressure in the vessels of the greater circulation, the left heart is not in a position to propel all the blood out of the pulmonary vessels. This means that the lesser circulation develops stagnation of the blood and a rise in the hydrostatic pressure (and, consequently, in the filtration pressure). As a result of the high filtration pressure and the rise in permeability of the pulmonary membrane, a serous fluid rich in proteins is forced from the blood in the pulmonary vessels into the alveoli. This disrupts the gas exchange in the lungs and causes death in severe cases. According to G. S. Kan (1953), the mechanism for the development of pulmonary edema is as follows. The intravenous injection of toxic doses of adrenalin produces an initial powerful stimulation of the chemoreceptors of the lesser circulation, the heart and adjacent vascular regions. Reaching the peripheral arterial vessels, the adrenalin causes a sharp rise in the level of arterial pressure as a result of spasms, mainly of the arterioles innervated by the splanchnic nerves. At the same time, the blood is redistributed. From the internal organs where the vessels are constricted, it flows out into the vessels of the skeletal muscles and the brain, a large portion going into the pulmonary vessels. As a result, there is a marked overfilling of the pulmonary vessels with blood, causing a discharge reflex: the excess fluid is removed from the lungs by means of protective mechanisms along the lymphatic vessels and by evaporation of the liquid which penetrates the alveoli. As the dose of adrenalin increases, this process increases quantitatively, but due to insufficiency of

the complex of protective mechanisms relieving the lesser circulation, the transudate (and later the hemorrhagic fluid) begins to fill a portion of the alveoli and then all the alveoli. It destroys gas exchange in the lungs, and the animals perish from the anoxemia and anoxia which develop.

The changes in hemodynamics with the development of adrenalin pulmonary edema have also been studied in rather fine detail (Cheng, 1958; Cheng and Jarret, 1958). These authors found that the intravenous injection of adrenalin causes constriction of the peripheral vessels, which leads in turn to hypotonia in the greater circulation, increasing the venous flow into the right heart and into the pulmonary artery. The pulmonary arterial pressure and the pressure in the auricles and ventricles increases significantly. As a result of the rise in pressure in the greater circulation, there is a sharp increase in the left heart which prevents efflux from the pulmonary veins. Due to the increase in the filling of the lungs with blood, the hydrostatic pressure is increased two-fold in their capillaries. This exceeds the oncotic pressure of the plasma. The pressure gradient between the pulmonary arteries and the left auricle decreases. The work of the right and left hearts begins to decrease following the initial increase, decreasing the minute volume. Under these conditions, pulmonary edema develops.

There are large amounts of data on the role of the nervous system in the /61
disruption of the permeability of the pulmonary membrane with the development of adrenalin pulmonary edema.

Effect of Vagotomy Upon the Development of Adrenalin Pulmonary Edema

The experiments of A. G. Kravchenko (1955, 1959a) on rabbits and cats (adrenalin injected intravenously, 0.3 - 0.5 mg/kg) showed that unilateral vagotomy has no effect on the progress of pulmonary edema, while bilateral vagotomy increases the intensity of its development. In the author's opinion, this is a consequence of the simultaneous exclusion of the afferent and efferent impulses, since exclusion of only the afferent fibers of the vagus

nerve by atropine (0.1 to 1.0 ml given i.v., 10 to 20 minutes prior to injection of adrenalin) had no effect on the course of edema. However, an increase in the function of the efferent fibers of the vagus nerves upon the injection of an anticholinesterase preparation of eserin in the majority of cases prevented the development of adrenalin pulmonary edema in the animals. Similar results with vagotomy were obtained by Wright and Whitten (1953).

A diametrically opposite outcome for experiments with preliminary vagotomy was observed by K. M. Bykov and his associates (1943a, b). Adrenalin was injected into rabbits 15 to 40 minutes after bilateral vagotomy. The majority of experimental animals failed to develop any pulmonary edema; in the others, the degree of edema was significantly less than in the controls, and it occurred later. The animals rarely died. Atropinization and unilateral vagotomy had no effect on the development of edema. The same result was observed in experiments using similar effects by G. S. Kan, 1953, with the exception of the fact that in his experiments the edema increased when large doses of atropine (1-5 mg for a rabbit) were given.

Bilateral vagotomy in the experiments of G. S. Kan retarded the development of edema to a lesser extent than in the experiments of K. M. Bykov, although the conditions for conducting the experiments were the same: adrenalin was injected 15 to 30 minutes after cutting the nerves in doses of 0.3 mg/kg or somewhat less. Seven out of the eleven experimental rabbits survived, and four died from severe pulmonary edema. It should be mentioned that the difference in the results of the experiments of these authors might depend on the fact that G. S. Kan used doses of adrenalin 1-1/2 to 2 times greater than did Bykov et al. Kan felt that a reduction in the development of edema following vagotomy is a consequence of exclusion of the afferent impulses passing from the lungs to the CNS. This conclusion is supported by the fact that exclusion of efferent endings of the vagus nerves by atropinization did not stop the development of pulmonary edema. However, an increase in the flow of afferent impulses produced by stimulation with electric current of the central segment of the vagus nerve, in conjunction with the i.v. injection of subthreshold doses of adrenalin, led as a rule to

severe pulmonary edema. At the same time, however, neither the stimulation of the nerve nor the injection of equal doses of adrenalin alone (without being combined) was able to produce edema.

The same point of view is supported by other experiments of G. S. Kan. /62 The injections of 20 ml of physiological solution with a fatal lethal dose of adrenalin into the carotid artery produced a sharp increase in arterial pressure, but it was not accompanied by the development of edema. The author concludes that the primary influence on the development of edema is exerted by the stimulation of chemoreceptors in the lesser circulation by adrenalin; other receptors, however, like the mechanical factor, play a secondary role. This is indicated by the fact that a combination involving stimulation of the central ending of the vagus nerve produced edema under the same experimental conditions.

Hence, unilateral vagotomy did not produce any effect on the development of adrenalin edema in all experiments. This may be explained by the presence of a chiasmic innervation of the lungs by the vagus nerves. Exclusion of the efferent fibers of the vagus nerves either had no effect on the progress of the edema or slightly increased it, but unilateral vagotomy in experiments of different investigators turned out to have a diametrically opposite effect on the development of adrenalin pulmonary edema. Although in some cases the contradiction of the data might be due to differences in methodology, it still remains unexplained why vagotomy caused opposite results under the same experimental conditions.

Exclusion of Sympathetic Nerves

In the majority of cases, this retarded the development of adrenalin pulmonary edema.

Luisada (1928) and G. S. Kan (1953) prevented pulmonary edema by cutting the spinal cord between the middle cervical segments. G. S. Kan feels that

this excluded the efferent pathway which passes from the CNS along the sympathetic nerve fibers to the lungs.

Boggian (1929) prevented adrenalin pulmonary edema by extirpation of one or both stellate nodes; Halpern and Roux (1949) prevented it by preliminary injection of sympatholytic substances (gynergen, dibenamine, dihydroergotamine, etc.). They were completely successful in preventing adrenalin edema in 35 rats by the preliminary injection of sympatholytin or animazine (Bymanova et al., 1956; Bymanova, 1957). In these same experiments, it was noted that pachycarpine (the blocker of N-cholinoreactive systems) had no effect on the development of pulmonary edema.

An inhibitory effect on the development of edema was observed by Glass (1928) when he removed the upper cervical sympathetic node.

Hence, removal of the efferent sympathetic nerves of the lungs, as a rule, prevents or retards the development of adrenalin pulmonary edema. The majority of experimenters feel that these nerves carry impulses from the CNS to the lesser circulation, allowing development of pulmonary edema. /63

Exclusion of Different Sections of the Central Nervous System

Depending of the level of the cut, this has different effects on the development of adrenalin pulmonary edema.

Luisada (1928) removed the cerebral cortex and corpus striatum 24 hours prior to the injection of adrenalin. Edema did not develop in two out of four rabbits. Decerebration under a mild ether anesthesia 10 to 15 minutes prior to injection of adrenalin prevented edema in the experiments of K. M. Bykov et al.(1943a, b).

G. S. Kan (1953) cut the brain either between the laminae quadrigeminae or at the level of the posterior laminae quadrigeminae under anesthetic (ether, urethane). Following decerebration, 45 to 100 minutes later, the

usual lethal dose of adrenalin was given. Fatal pulmonary edema was observed in all the rabbits.

Contradictory results were obtained under similar conditions by A. G. Kravchenko (1955, 1959a, b). Decerebration between the laminae quadrigeminae or at the level of the posterior laminae quadrigeminae prevented development of pulmonary edema in 9 out of 13 cats and in 9 out of 10 rabbits.

All of these experimental data have led the majority of investigators to conclude that the development of adrenalin pulmonary edema means that the reflex arc that begins in the vascular receptor zones can be closed at the level of the brain stem.

A clear example of the participation of the nervous system in the development of adrenalin pulmonary edema is the fact that this form of edema is very difficult to produce in the early post-natal period of development of animals. During this period, the nervous system has not yet been completely formed, and many reflexogenic zones are not functioning; the nervous system is areactive to many stimuli (Arshavskiy, 1936, 1952, 1967; Kositskiy, 1949b).

With this in mind, A. G. Kravchenko (1959b, c) studied the development of pulmonary edema in young puppies. Injection of 0.005 to 0.1% solution of adrenalin per kg of body weight did not produce pulmonary edema in puppies 1 to 10 days old. At the age of 10 to 20 days, an insignificant edema arose at the same doses. At later stages, the same dose of adrenalin produced severe pulmonary edema. The absence of pulmonary edema in the puppies when large doses of adrenalin were injected is explained by the author as due to insufficient function of the receptor zones of the cardiovascular system (sino-carotid and cardio-arterial). During this period, there is also an absence of reactions of the respiration and blood circulation to the stimulus of afferent fibers of the vagus nerve (Polosukhin, 1948; Arshavskiy, 1936), but the efferent effects of the vagus and sympathetic nerves on the cardiovascular system are present (Kositskiy, 1949b).

According to the data of S. I. Yennikeyeva (1945), the lethal dose of adrenalin for puppies is 8 to 10 times greater than for adult dogs. The lethal dose of adrenalin for baby rabbits up to 12-15 days old is 20 to 30 times greater than for adult rabbits. Similar results under the same experimental conditions were obtained by G. S. Kan (1953). Hence, there is every reason to assume that the participation of the reflex central apparatus of the nervous system is necessary for the development of adrenalin edema of the lungs. /64

A necessary condition for the development of pulmonary edema from any cause is disruption of the permeability of the pulmonary membrane.

An indirect indication of an increase in permeability of the pulmonary membrane with development of adrenalin pulmonary edema and also the fact that its development is not necessarily a consequence of an increase of hydrostatic pressure is indicated by the observations of G. S. Kan (1953), Halpern et al. (1950) and K. M. Bykov et al. (1943 a, b).

Thus, in the experiments of G. S. Kan which involved intra-arterial injection of adrenalin, the arterial pressure rose more sharply than in the case of intravenous injection of the same substance at the same doses, but no pulmonary edema developed. Halpern, et al.(1950) demonstrated the possibility of preventing adrenalin pulmonary edema by a preliminary injection of phenergan with complete retention of a pronounced rise in pressure in the right ventricle and the greater circulation.

In the experiments of K. M. Bykov, et al.(1943a, b), decerebration prevented the development of edema, although the pressure rose to the same degree as in the intact animals when adrenalin was injected into the experimental rabbits.

Indirect indications of an increase in permeability of the pulmonary membrane with development of adrenalin pulmonary edema include the observations of Trendelenberg (cited in Ya. A. Lazaris and I. A. Serebrovskaya (1962) showing that subcutaneous injection of large doses of adrenalin causes pulmonary edema without hypertension or with a very moderate increase in blood pressure.

Direct indications of disruption of the permeability of the pulmonary membrane with the development of adrenalin pulmonary edema were given by Hayek (1953) and Kisch (1958a, b). Using an electron microscope, Kisch observed structural changes in the membrane analogous to those which were described by Meessen and Schulz in 1957 in other forms of pulmonary edema.

Hence, adrenalin pulmonary edema, like edema from other causes, is the /65
consequence not only of changes in hemodynamics, but also of disruption of permeability of the pulmonary membrane. In this respect, obviously, both changes in hemodynamics and disruptions of permeability have reflex origins.

Gelhorn (1932), G. S. Kan (1953), A. I. Il'ina (1952), Luisada (1928) and A. V. Tonkikh (1949) and other authors feel that an increase in permeability arises due to increased flow of efferent impulses coming along the sympathetic nerves to the lungs. Thus, A. V. Tonkikh showed that stimulation of the peripheral end of the vagus nerve does not produce changes in the permeability of the pulmonary vessels, while stimulation of the sympathetic system (crushing of the upper cervical nodes) produced pulmonary edema and pneumonia.

G. S. Kan, investigating the role of the nervous system in the pathogenesis of pulmonary edema, concluded that a critical role in its development is played by reflex mechanisms. He proposed the following reflex system for the production of edema: adrenalin, injected intravenously, stimulates the chemoreceptors of the lesser circulation and, by increasing the blood pressure, causes irritation of the baroreceptors in the lesser circulation and other reflexogenic zones. The flow of impulses along the

afferent fibers of the vagus nerves reaches the brain stem and then moves on along the descending pathways of the spinal cord; the impulses then pass into the pulmonary vessels through the marginal sympathetic chain, promoting the development of edema.

Effect of Supplementary Nonspecific Stimuli on the Development of Adrenalin Pulmonary Edema

Hence, an analysis of the literature on the pathogenesis of adrenalin pulmonary edema brings us to the conclusion that an important role in the development of this pathological process must be assigned to the nervous system. There are many data which show that stimulation of the nervous system by various stimuli can have a significant effect in changing the course of pulmonary edema.

Thus, G. S. Kan (1953), in his experiments on rabbits, injected adrenalin intravenously in doses that were 37 to 45% less than the usual toxic lethal dose. Immediately after injection, electric current was used to stimulate the central end of the formerly prepared and sectioned sciatic nerve. The animals died in 4 to 15 minutes from severe hemorrhagic pulmonary edema.

In our experiments, we prepared the sciatic nerves of six rabbits. They were connected to platinum electrodes attached to the secondary coil of a Dubois-Raymond apparatus. Adrenalin was injected into the ear vein for 30 seconds at a dose that was used by G. S. Kan (1953), Table 1. In 3 to 12 minutes after injection of adrenalin, the sciatic nerves were stimulated by an impulse of electric current from the induction coil (the voltage on the primary was 2 to 4 V, and the distance between the windings was 9 to 13 cm). /66 Severe pulmonary edema rapidly developed when the current stimulus was applied. The results of this group of experiments were similar to those described in the data of Kan. We showed however that the development of edema is dependent on the time of application of the supplementary non-specific stimulus (electric current).

TABLE 1. DOSES OF ADRENALIN PRODUCING PULMONARY EDEMA IN RABBITS (INTRAVENOUS INJECTION)

Rabbit wt., g	Adrenalin dose, mg		Rabbit wt., g.	Adrenalin dose, mg	
	For animal as a whole	Per kg body wt		For animal as a whole	Per kg body wt
	Luisada (1928)	G.S. Kan (1953)		Luisada (1928)	G.S. Kan (1953)
1400	0,40	0,42	1800	0,55	0,55
1500	0,45	0,45	1900	0,55	0,55
1600	0,45	0,45	2000	0,55	0,6
1700	0,50	0,55			

In those cases when the stimulation of the sciatic nerves preceded the injection of a toxic dose of adrenalin, it prevented development of pulmonary edema. This was clearly demonstrated in the experiments on seven rabbits with the aid of the method described above.

The current strength was set so that the animals responded with a motor reaction only during the first moments of action of the current, then remained quiet during the experiment (the distance between the windings was 9-13 cm, and the primary voltage was 2-4 V). The problem of the strength of the stimulus plays an extremely important role in these experiments, so that it must be discussed in greater detail.

As we know, I. P. Pavlov observed that irradiational concentration of any nervous process in the cortex of the cerebrum caused by the action of any kind of stimulus depends on the strength of the latter. A weak (for a given nervous system) stimulus produces a weak excitation process which has the ability to irradiate (occupying other points). A rather strong (for a given nervous system) stimulus leads to the development of a strong process

of excitation which has the ability to concentrate at the point of development. This is accompanied by the appearance of a negative induction, i.e., processes of inhibition in other points in the CNS. A still stronger (for the given nervous system) stimulus produces the phenomenon of a strong excitation process which again begins to irradiate, thereby occupying the entire CNS. Generalization of the excitation process then occurs.

We found in our studies that in order to inhibit adrenalin pulmonary /67
edema, it is necessary to use rather strong stimuli which produce a concentration of the process of excitation at the original point in the central nervous system and phenomena of negative induction (inhibition) at other points. This state is manifested externally by the development of phenomena of inhibition and motor cramps (numbness) of the animal. The administration of a pathogenic stimulus against the same background does not lead to the development of the pathological process. However, in the event that the force of a "supplementary" (nonspecific) stimulus is insufficient and the state of total paralysis of the animal (stupor) does not develop (i.e., when the motor activity is not inhibited as the stimulus is applied and does not change noticeably, no inhibition of pathological processes takes place).

The same unsuccessful outcome is observed in those cases when the force of the "supplementary" (nonspecific) stimulus is excessive and leads to generalization of the excitation process, occurring in the form of a sharply increased motor activity, which changes to general muscle spasms. Therefore, an important condition in these experiments is the fact that the intensity of the supplementary stimulus must be selected individually so that it evokes general inhibition (stupor) of the animal. Ignoring this fact could be the cause of a lack of success in similar experiments, since inhibition of pathological processes is not then possible.

Three to nineteen minutes after application of the current, and against the background of its action, a toxic dose of adrenalin was given in the ear vein of a rabbit.

The animal continued to be under the continuous action of the current for 10 to 20 minutes after the injection of adrenalin. Six rabbits in this group, which did not die of pulmonary edema, were sacrificed, and the autopsies of five of them failed to show any edema (the pulmonary coefficient was 4.5 to 5.5), while one showed traces of edema (pulmonary coefficient — 6.3[1]). The seventh rabbit, before injection of adrenalin, was impossible to put into a quiet state. It was excited during the experiment and died showing symptoms of edema (pulmonary coefficient — 7.3).

Consequently, the same supplementary reflex (the effect of faradic current on the sciatic nerve) produced contradictory effects on the outcome of the pathological process, depending on whether or not it was preceded by the action of a pathogenic stimulus or followed it.

Similar phenomena were observed in other experiments, especially in an /68
investigation of the action of artificial respiration on the development of adrenalin pulmonary edema. In the experiments of G. S. Kan (1953), forced artificial respiration prevented the development of pulmonary edema; the author therefore even proposed that this method be used for treating severe pulmonary edema. We repeated these experiments, changing only the periods of application of artificial respiration.

In five rabbits, the switching on of artificial respiration preceded the injection of adrenalin by several minutes or was begun at the same time that the adrenalin was injected and lasted for 10 to 15 to 20 minutes more. Not one of these five rabbits developed pulmonary edema. The pulmonary coefficient was 3.68-5.

In the next group of experiments, on five rabbits, the trachea was prepared and a cannula inserted. Artificial respiration was not connected;

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[1] The pulmonary coefficient is the ratio of the weight of the lungs in grams to the body weight in kilograms, normally equal to 4.0-5.0 in the rabbit.

the animals simply breathed through the cannula. Adrenalin was injected intravenously and five minutes after injection (when the development of edema was usually observed to begin in the control experiments), forced artificial respiration was applied. All five rabbits died several minutes after the artificial respiration was connected, with symptoms of severe pulmonary edema (the pulmonary coefficient was 8.5 to 11). Thus, in the case of incipient edema, forced artificial respiration not only was not a method to use in therapy, but might even have sped up the death of the rabbits.

This same method, used prior to the injection of adrenalin or at the time the latter was injected (prior to the beginning of development of edema) prevented the development of edema. The mechanism of its action lies not only in the influence which it exerts on the processes of gas diffusion in the alveoli, but also in the fact that artificial respiration is a strong stimulus for the receptors of the respiratory pathways and the lungs themselves. Hence, here again the outcome of the pathological process depends on the interaction during pathogenic and supplementary stimuli.

In our opinion, stimulation of the receptors during artificial respiration regularly inhibits the induction of the central branches of the reflex reactions participating in the development of edema. With artificial respiration, applied after adrenalin is injected, the stimulus from the forced artificial respiration apparently reinforces the dominant foci of the reflex reactions participating in the development of the edema, increasing the intensity of this process. This assumption seems to us to be the most satisfactory explanation for the experimental data obtained. Forced artificial respiration should therefore never be recommended as a method of treating edema (Kositskiy, 1954).

Development of Adrenalin Pulmonary Edema in the Case of Stimulation of the Peritoneal Receptors by Injection of Turpentine, Fish Oil and Air into the Peritoneal Cavity

Turpentine (2-6 ml) was injected into the peritoneal cavity of five rabbits; a sixth animal received a significantly larger amount, 14 ml. Two to five minutes after injection of the turpentine, a toxic dose of adrenalin was administered intravenously. The first five rabbits did not develop pulmonary edema (the coefficient was 3.5-5.2), while the sixth rabbit (which was given the 14 ml of turpentine) died five minutes after injection of adrenalin, showing symptoms of severe pulmonary edema (pulmonary coefficient — 12.7). /69

Consequently, stimulation by turpentine of the peritoneal receptors prevented the development of pulmonary edema. The injection of overly large amounts of turpentine (14 ml) did not prevent pulmonary edema. In two experiments involving the injection of turpentine after adrenalin, the pulmonary did develop. Prevention of edema in this case can apparently be explained by the fact that the turpentine does not act as a specific "antidote", but as a "distracting" device, with the result depending on the time of application of this supplementary stimulus.

Mild stimulus of the peritoneal receptors (injection of 80-90 ml of air in four experiments and 14 ml of fish oil in one) did not prevent the development of pulmonary edema.

The effect of the action of a supplementary nonspecific stimulus on the development of pulmonary edema was studied in a special series of experiments in which the stimulus was the production of artificial pneumothorax.

As we know, insufflation of air into the pleural cavity produced a sharp stimulation of the extensive receptor field of the pleura (Kositskiy,

1955; Kochergan, 1953, 1957). In this regard, we used pneumothorax as a supplementary stimulus in experiments with adrenalin pulmonary edema.

In the control experiments (13 rabbits), adrenalin was injected into the jugular or ear vein for 5 to 15 seconds in the doses suggested by Luisada (1928). We recorded the blood pressure and the respiration. Nine rabbits in this group died 5 to 15 minutes after injection of adrenalin, after developing spasmodic asphyxic respiration and with the appearance of a frothy liquid in the upper respiratory pathways. With the same symptoms, however, the four remaining rabbits did not die in the same period of time and were killed. After opening the rib cage, it was found that the lungs of all the animals that had died or were sacrificed were swollen and did not collapse; they had a spotted or marbled appearance, due to alternating dark red, cherry-colored and rosy emphysematous areas. A large amount of frothy fluid flowed from the surface of the incision. The trachea and bronchi were also filled with this foamy liquid. The pulmonary coefficient, normally 4.0 to 5.0, was 8.3 to 12.5 in all experiments, indicating an increase in the weight of the lungs by a factor of two or three relative to normal. Hence, the generally assumed use of adrenalin in all 13 control experiments promoted the development of severe pulmonary edema. In the basic experiments of this series, we studied the influence of pneumothorax on the development of pulmonary edema. We /70 injected 10 to 60 cc of air into the pleural cavity of rabbits for 15 to 30 seconds. After producing artificial pneumothorax, X-rays were made of the chest cavity; many showed air bubbles and the edge of the collapsed lung (Figure 10A). Adrenalin was injected into the ear vein at different times after the production of artificial pneumothorax (from 5 minutes to 3 hours and 10 minutes later).

In the majority of cases, artificial pneumothorax protected the animals from the development of edema in the case of those rabbits which (after the injection of 25 to 40 cc of air with the formation of additional collapse of the lungs) showed retention of negative pressure in the pleural cavity. Twelve out of 19 experiments did not even show any traces of edema (pulmonary coefficient — 3.5 to 5.95, with a normal of 4 to 5) and only the remaining 7

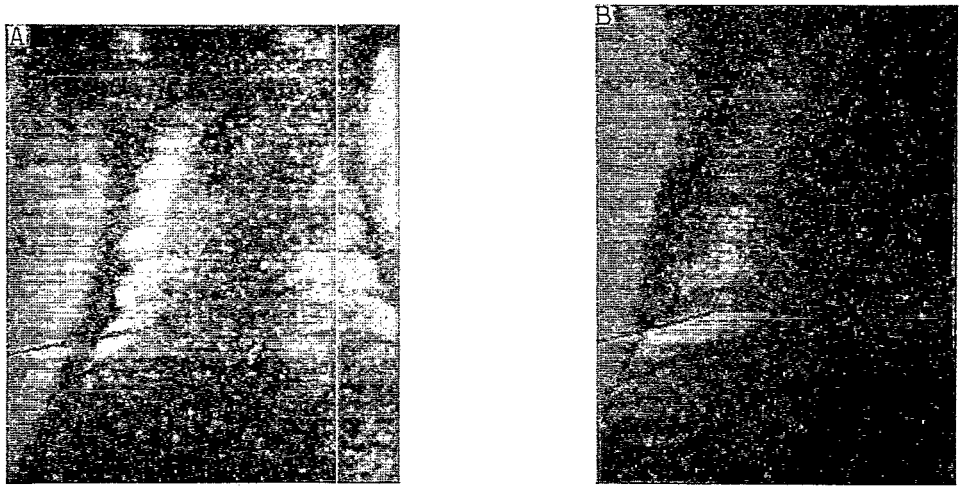

Figure 10. X-rays of chest cavities of rabbits after creation of artificial pneumothorax: A - Small air bubble; B - Enormous air bubble.

experiments showed development of very small degree of pulmonary edema, much less than in any of the control experiments (pulmonary coefficient — 6.33 to 7.2).

Consequently, the induction of artificial pneumothorax prevented the animals from developing pulmonary edema upon the injection of a toxic dose of adrenalin. Even when the lethal dose of adrenalin was increased in the subsequent six experiments by 3 to 4 times, edema did not develop in three of the experiments, even with artificial pneumothorax, while in the other three experiments a relatively slight edema was seen.

It is doubtful whether the collapse of the lung in these cases was only a simple mechanical factor that prevented the occurrence of edema. As we know, collapse of the lungs produces conditions for blood stagnation which can of themselves promote the development of edema. In our experiments, however, collapse of the lungs prevented the development of edema. The suggestion of "compression" as a mechanical direct preventative measure for edema was also checked in a group of experiments where the injection of large amounts of gas

into the pleural cavity took place. X-rays in these experiments showed an immense air bubble and a considerable area of collapsed lung (Figure 10B).

In four cases, when 45 to 60 cc of air were injected, regardless of the enormous bubble and the considerable collapse of the lung, edema of both lungs developed. In exactly the same manner, edema developed in one case in the case of insufflation of 10 cc of air when collapse was so slight that it could not be determined by the use of X-rays and the pressure in the pleural cavity, which was 2 to 3 cm H_2O prior to artificial pneumothorax, did not change after insufflation, but only occurred in another case, when a relatively small bubble was observed, and the pressure in the pleural cavity remained the same as before insufflation. This indicates that it is not a mechanical factor that prevents the development of edema of the lungs, and that artificial pneumothorax in these experiments had a reflex effect and not a mechanical one. It should be mentioned that to inhibit the pathological /71
effect of adrenalin, it is only necessary to have a certain optimum degree of collapse, i.e., here, too, there is a quite distinct picture of the significance of the factor of the strength of the supplementary stimulus. It is interesting that unilateral artificial pneumothorax prevented to a unique degree the development of edema in both lungs. However, in those cases when edema still developed, it was equally severe in both lungs, regardless of the side on which the artificial pneumothorax was created.

It is clear from the data given above that artificial pneumothorax causes an adjustment of the organism such that a marked effect of adrenalin on pulmonary receptors, causing the usual development of pathological reflex edema of the lungs, does not lead to development of this reflex (Kositskiy, 1955).

Would it be interesting to find out to what extent similar results could be obtained on other animals using other supplementary nonspecific stimuli? In this connection, experiments were conducted with white mice, white rats and guinea pigs. Working with small animals made it easier to apply the experiments to a large number of animals.

We determined the reliability of the difference between the pulmonary coefficients and the survival time of the experimental and control animals.

For the mice, rats and guinea pigs, the toxic doses of adrenalin were selected empirically and were as follows: for mice, 0.105 to 0.022 mg adrenalin were given to animals weighing 18 to 22 grams, injected into the /72
tail vein in 0.10 to 0.20 ml of physiological solution for 5 seconds; for guinea pigs and rats, the dose was 0.2 to 0.3 mg/kg of body weight in 0.20 to 0.30 ml of physiological solution in the jugular vein (the veins were prepared beforehand, not using anesthesia). After i.v. injection of the above doses of adrenalin, the control animals died as a rule, the mice in 1 to 3 minutes and the rats and guinea pigs in 5 to 10 minutes.

Development of Pulmonary Edema in Rats, Mice and Guinea Pigs with Stimulation of the Animals by an Electric Current

Experiments on mice (31 animals) were conducted according to the following method: the animals were held in a supine position and subjected to the stimulus of an electric current. The electrodes were applied to the abdominal cavity, so that under the influence of the current the entire peritoneal wall, including the peritoneum, was subjected to the influence of the current from an electronic stimulator (current strength 3.5 to 5.0 mA, pulse frequency 42 Hz). Fifteen to twenty minutes after the start of stimulation, a toxic dose of adrenalin was injected into the tail vein against the background of the action of the current.

The results of these experiments showed that stimulation of the peritoneal wall in mice by an electric current reduced the development of adrenalin pulmonary edema by 10 to 75% in half the cases, in comparison to the control animals, which received only adrenalin.

The average pulmonary coefficient (PC) in the experimental animals (20.8 ± 1.99) was insignificantly less than for the controls (22.8 ± 0.776), but the survival rate of the experimental animals was statistically reliably

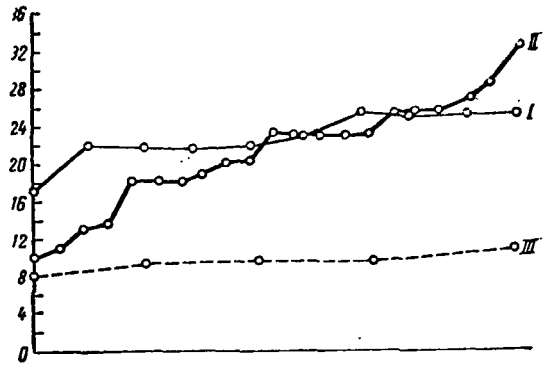

Figure 11. Value of pulmonary coefficient in mice: I - After injection of adrenalin (10 mice, 1 survivor); II - After injection of adrenalin with action of electric current (21 mice, 11 survivors); III - Without injection of adrenalin (5 mice).

higher: out of 10 control animals, one survived, but 11 out of 21 experimentals. These results support the data obtained earlier. This is illustrated by the variation curves (Figure 11), which were plotted as follows. All cases (experiments) of a given group were arranged in order of increasing pulmonary coefficient, whose values are indicated on the graph by points.

In this case, however, the abscissa is divided into equal segments, corresponding in number to the number of cases (experiments) in the group which made up a given variation series. The line linking the points of a given variational series reflected the value of the pulmonary coefficient in a given group of experiments.

For each group of experiments, a specific variational series was plotted in precisely this manner (and accordingly, its curve), with the scale on the coordinate (reflecting the value of the pulmonary coefficient) not being changed, but the number of segments into which the axis of the abscissa was divided changed from group to group according to the number of experiments in a given group for each case.

In similar experiments on rabbits, we obtained much more pronounced inhibitory effects of the supplementary stimulus on the development of adrenalin pulmonary edema. This difference in the outcome of the experiments has been explained until now by the fact that the experiments were performed on different kinds of animals. In order to check this theory, the following /73 series of experiments was performed on rats.

The results of the experiments which were conducted according to the same system as for mice and rabbits showed that the development of pulmonary edema in rats under the action of an electric current was also inhibited insignificantly. The pulmonary coefficient in the experimental animals was only slightly less (21.2 ± 1.46) than in the controls (25.4 ± 1.38). Six animals out of 15 experimentals survived, while only 2 out of 14 controls lived.

In similar experiments on guinea pigs, the electric current in all cases reliably reduced the intensity of development of adrenalin pulmonary edema and raised the survival rate of the experimental animals. The results of these experiments will be discussed in greater detail in Chapter IV.

Hence, with a single pathological process caused by a single pathogenic agent (adrenalin), the action of a given supplementary stimulus (electric current) affects the development of a pathological process with different effectiveness in different kinds of animals. In this connection, it was interesting to find out whether or not the same difference exists in the reactions of organisms of different animals to nonspecific stimuli (for example, turpentine and formalin).

Development of Pulmonary Edema in Rats with Subcutaneous or Intraperitoneal Injection of Formalin

To study the effect of formalin as a supplementary stimulant on the development of adrenalin pulmonary edema, we performed experiments on 24 rats, 11 of which were experimentals and received injections of formalin and adrenalin, and 13 controls, which received adrenalin alone.

The structure of the experiment was the usual: 0.3 ml of 4% formalin was injected into the peritoneal cavity or 0.7 ml was injected beneath the skin of the leg, and sometimes at four points simultaneously. When this was done, pulmonary edema was inhibited to the greatest degree.

Twenty to forty minutes after injection of formalin, we injected a toxic /74 dose of adrenalin i.v. (0.2 mg/kg of body weight for rats). The development of pulmonary edema in the experimental rats in comparison to the controls was significantly retarded. The pulmonary coefficient in the experimental animals was equal to 12.2 $\pm$ 0.4, while in the controls it was 20.6 $\pm$ 1.1. All 11 experimentals survived (100%), while only five of the 13 controls survived (38.5%). The differences in PC (P_1) and survival rate (P_2) between the controls and the experimental animals were statistically reliable (P_1 less than 0.001; P_2 less than 0.001).

Thus, formalin, as a supplementary nonspecific stimulus, has a more effective inhibitory effect on the development of adrenalin edema of the lungs in rats than electric current.

Development of Pulmonary Edema in Guinea Pigs, Rats and Mice under the Influence of Turpentine

We initially tested the effect of turpentine alone in these animals. During the first minutes following its injection subcutaneously into the peritoneal cavity, the animals showed excitement, accompanied by a general motor reaction. Several minutes later, excitement was replaced by general stupor. During this period, mild mechanical stimulus of the skin as a rule did not produce any reaction; the animals moved sluggishly and there was a slowdown of respiratory movements. Two to four hours later (depending on the dose), the mice died. The rats and guinea pigs lived under such conditions for hours and days. The lungs of the animals which died showed phenomena indicating stagnation, and sometimes there was insignificant edema.

The first series of experiments was conducted on 11 guinea pigs, 5 of which were controls (i.e., they received only adrenalin). The experimental animals received turpentine as the supplementary stimulus: 0.2 ml in the peritoneal cavity, 15 to 24 minutes prior to the injection of a toxic dose of adrenalin (0.2 mg/kg, i.v.). The results of this series of experiments are shown in Table 2.

TABLE 2. DEVELOPMENT OF PULMONARY EDEMA IN GUINEA PIGS WITH INJECTION OF TURPENTINE INTO PERITONEAL CAVITY AND ADRENALIN GIVEN INTRAVENOUSLY

Control				Experiment				
Expt. No.	Adrenalin, mg/kg	Result	Pulmonary coeff.	Expt. No.	Turpentine, ml	Adrenalin, mg/kg	Result	Pulmonary coeff.
14	0,25	Death	19,2	11	0,2	0,30	Survived	7,1
15	0,25	»	26,0	18	0,2	0,20	»	7,7
17	0,20	»	20,1	19	0,2	0,20	»	6,2
21	0,20	»	19,0	20	0,2	0,20	»	8,0
23	0,20	»	24,0	22	0,2	0,20	»	6,6
				24	0,2	0,20	»	8,9

It is clear from the table that all six experimental animals which received turpentine before adrenalin, survived and pulmonary edema essentially did not develop in any of them. This is indicated by the pulmonary coefficient, which is almost the same as for the experimentals (7.4 ± 0.368) and the intact, healthy animals (6.5 ± 8.5). All 5 control guinea pigs, which received only adrenalin, died with symptoms of intense pulmonary edema (pulmonary coefficient 21.7 ± 1.263). The difference in the pulmonary coefficient and in the survival rate between the experimentals and the controls was statistically reliable (P_1 less than 0.001; P_2 less than 0.001).

A second series included experiments performed on 22 rats. Turpentine was injected in amounts of 0.3 to 0.5 ml into the peritoneal cavity, 20 to 40 minutes prior to injection of a toxic dose of adrenalin (0.4 mg/kg body weight) in the jugular vein.

The supplementary stimulus, even in experiments on rats, inhibited the /75 development of pulmonary edema to a considerable degree, as indicated by the

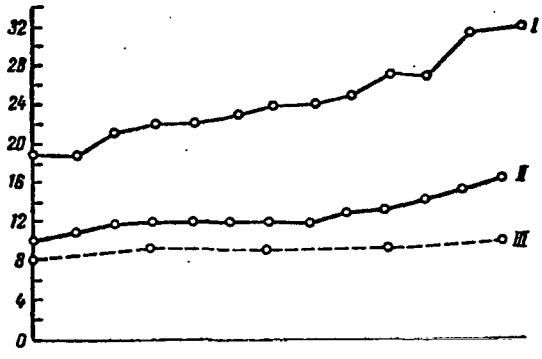

Figure 12. Value of pulmonary coefficient in mice. I - After injection of adrenalin; II - After injection of turpentine and adrenalin; III - No adrenalin (5 mice).

comparitively small PC for the experimental animals (14.2 $\pm$ 1.39; it was 6 to 8 for the healthy animals). Out of 12 experimental animals, 9 survived (75%); at the same time, however, all 10 controls which had received only adrenalin died from severe pulmonary edema (pulmonary coefficient 25 $\pm$ 1.37). The differences were statistically reliable (P_1 less than 0.001; P_2 less than 0.001).

It is necessary to note that turpentine inhibited the development of adrenalin pulmonary edema in rats to a lesser degree than in guinea pigs.

The third series of experiments was conducted on 54 white mice. The turpentine was injected in amounts of 0.05 to 0.5 ml into the peritoneal cavity 10 to 15 minutes prior to the injection of a toxic dose of adrenalin (0.020 to 0.030 mg/animal, weighing 18-22 grams). The results of the experiments indicate that the supplementary stimulus almost completely prevents the development of adrenalin pulmonary edema. This is indicated by the low pulmonary coefficient (13.4 $\pm$ 0.5) which exceeds the pulmonary coefficient of intact mice by only 3 to 4. Of the 32 experimental mice, 28 survived, while all 22 control animals (which did not receive any turpentine) died of severe pulmonary edema (pulmonary coefficient 23.1 $\pm$ 0.92). The difference between the experimental and control animals was reliable (P_1 less than 0.01; P_2 less than 0.01). The above is illustrated by the variation curves in Figure 12. /76

Hence, in all experiments in which the action of a supplementary nonspecific stimulus prevented the action of the pathogenic stimulus, we observed the sharp inhibition of pathological processes.

In cases when the action of supplementary nonspecific stimulus was applied following the action of a pathogenic stimulus, inhibition of the pathological process was not observed. Instead, in the latter case we often observed even a more intensive (in comparison to the control experiments) development of the pathological process.

The data which we obtained, it seems to us, indicate a nervous rather than a humoral nature of effects of supplementary stimuli. The reflex mechanism of these effects is indicated by their dependence on the intensity of the supplementary nonspecific stimulus and the sequence of action of the specific and nonspecific stimuli.

It seems to us that nonspecific stimulation of a certain intensity forms a focus of dominant stimulation in the CNS, thanks to which the remaining reflex reactions of the organism are inhibited to a greater or lesser degree (not having any relationship to the given dominant stimulus). Then, apparently, the reflex components of all the above-described pathological processes are inhibited, which makes it possible to prevent their development (Kositskiy, 1956 b, 1962b).

However, in describing similar phenomena, Selye says that the increase in resistance and the prevention of development of pathological processes in these cases are dependent on the intensification of the activity of the endocrine glands (the hypophysis-adrenal system) and adaptive hormones which are injected into the blood. In talking about the "chiasmic resistance", Selye states that the adaptive hormones which are produced under the influence of stressors raise the resistance of the organism relative to the action not only of these stressors, but of other pathogenic stimuli as well.

Since the differences in evaluating the observed phenomena are very important for this work, it is necessary, first of all, to describe in greater detail the basic tenets of the school of G. Selye. After that, we shall give some data on the results of experimental tests of this concept, using several models of pathological processes.

CHAPTER III

DO SELYE'S CONCEPTS EXPLAIN THE PHENOMENON OF "NONSPECIFIC RESISTANCE"?

"Stress" Reaction Mechanisms and "Nonspecific" Resistance

In 1936 there appeared in one of the journals a brief article by the young investigator, Hans Selye, entitled, "A Syndrome Produced by Various Stimulating Agents." This paper presented data on the standard reactions of an organism under the influence of completely different pathogenic agents. Several aspects of these reactions were reminiscent of the changes described by A. D. Speranskiy (1935) under the rubric of "standard forms of nervous dystrophies" and often observed by I. P. Pavlov in dogs after traumatizing operations on the gastrointestinal tract. In this and later works, Selye (1956, 1960, 1967) wrote that the action of any harmful agent in rats caused the development of severe ulceration of the gastrointestinal tract and many other trophic disorders, accompanied by an increase in the activity of the adrenal cortex, involution of the thyroid gland and lymphatic apparatus, lymphopenia, eosinopenia and polymorphonuclear leucocytosis. /77

Selye labelled these phenomena of nonspecific reaction of the organism to the action of any harmful agent "stress" (using the English word), while the various irritant agents causing this reaction were referred to as "stressors".

According to Selye, "stress" consists of a general adaptational syndrome (GAS), a reaction which increases the resistance of the organism to the action of any harmful agent. Such an increase in resistance, in Selye's opinion, is linked to an increase in the function of the adrenal glands — the pituitary and the adrenal cortex. A "stressor", acting on the organism or any part of it, causes damage to tissues and the excretion of a "metabolite". The "metabolite" acts on the pituitary and causes an increase in the secretion

of hormones from its anterior portion: somatotropic hormone (STH) and adrenocorticotropic hormone (ACTH). The latter acts on the adrenal cortex, causing an increase in secretion of two types of hormones — mineralocorticoids and glucocorticoids.

The mineralocorticoids (desoxycorticosterone, etc.) regulate mineral exchange and further the retention of sodium in the organism. They exert an "inflammatory" effect, intensifying the inflammatory reaction under the influence of harmful agents. /78

The glucocorticoids (cortisone, hydrocortisone, etc.) act on the protein, fat and carbohydrate metabolism. They promote protein breakdown in organs and tissues, and lead to an increase in the amount of amino acids and blood sugar. These hormones inhibit allergic and inflammatory reactions and were called "anti-inflammation" hormones by Selye.

According to Selye, the increased secretion of these "adaptive" hormones ensures a change in the reactivity of the organism, i.e., an increase in resistance to the action of various stressors (Figure 13).

The development of a general adaptational syndrome has three stages, according to Selye:

1) The "anxiety stage", or the one in which the adaptation reaction occurs, when the "stressor" begins to cause increased production of ACTH and adrenal hormones; the resistance of the organism rises after an initial decline.

2) The "resistance stage", characterized by intensive production of adaptive hormones, leading to a further steady increase in the resistance of the organism;

3) The "exhaustion stage", in which there is an exhaustion of the pituitary and the adrenal cortex, a sharp decline in the production of

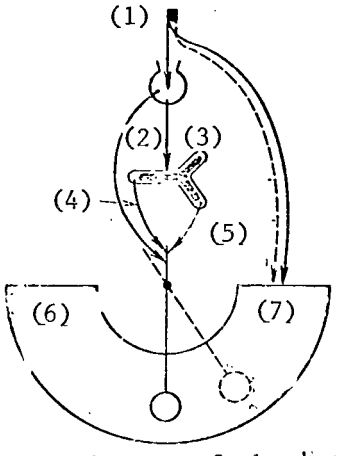

Figure 13. Diagram of the "stress" reaction (according to Selye). (1) Agent; (2) STH; (3) ACTH; (4) Inflammatory corticoids; (5) Anti-inflammation corticoids; (6) Danger: inflammation nephrosclerosis, hypertonia, etc.; (7) Danger: infection, necrosis, thymolysis, lympholysis, catabolism, etc.

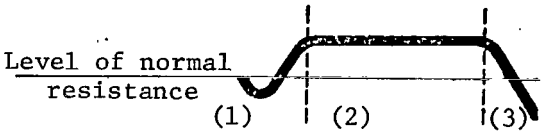

Figure 14. Changes and resistance (heavy curved line) in different stages of "stress": (1) - Anxiety reaction; (2) - Stage of resistance; (3) - Stage of exhaustion (according to Selye).

adaptive hormones and a marked decrease in the resistance of the organism (Figure 14).

The state of the pituitary-adrenal cortex system, according to Selye, /79 determines the level of the protective reactions of the organism, as well as the nature of the course of the pathological process or illness.

Selye suggests, in particular, that the state of "stress" that develops under the influence of any "stressor" raises the resistance of the organism, not only to the given "stressor", but to other pathogenic stimuli at the same time. Selye called this ability of the organism (1961) "chiasmic resistance". The concepts of H. Selye regarding "stress" have been widespread in the last 20 years. Many thousands of studies have been devoted to these concepts.

After the work of Selye, any increase in the resistance of the organism which developed in response to the action of any supplementary nonspecific stimuli was treated by many authors as a direct proof of the validity of

Selye's concept regarding "stress" and "chiasmic resistance" and the participation of "adaptive hormones" of the adrenal cortex in these processes.

Meanwhile, much of the information which we have gained shows that the increase in resistance of the organism under the influence of supplementary nonspecific stimuli cannot be explained from the standpoint of Selye's concept and do not support the basic views of this concept. We obtained information of this kind in our experiments with adrenalin pulmonary edema, anaphylactoid reactions and other pathological processes, i.e., in precisely those models which were widely employed by Selye and his followers as the basis for the concept of "stress".

Selye's Concept and Adrenalin Pulmonary Edema

Selye (1938-1952) observed an increase in the resistance of animals to toxic doses of adrenalin in experiments with preliminary exposure to cold, formalin and other "stressors". He felt that the increase in resistance observed under these conditions occurred as a result of an increase in the production of corticosteroids (Selye, 1952, 1960, 1961).

We know that the production of corticosteroids is regulated by a hormone produced by the anterior section of the pituitary (ACTH). Inasmuch as the present paper is a detailed study of the problem of whether hormonal mechanisms are involved in the prevention of the development of adrenalin pulmonary edema under the influence of supplementary nonspecific stimuli, we must spend some time in discussing the current concepts regarding the regulation of ACTH production.

Several theories exist at the present time regarding the mechanism of /80
regulation of the production and secretion of ACTH into the blood. In 1922, Cannon showed that the action of any stimulus (for example, pain) on the organism causes excretion of adrenalin from the adrenal cortex. According to Long (Gershberg, Long, 1950) adrenalin acts directly on the anterior lobe of the pituitary, stimulating the production of ACTH. This view is uncertain,

and at the present time the possibility of a direct action of adrenalin on the pituitary is disputed. Adrenalin plays an important role in the activation of secretion of hypothalamic neurohumors, which in turn stimulates the anterior lobe of the pituitary (Ingle, 1956; Utevskiy, Barts, 1964; Eskin, Shchedrina, 1964; Rothballer, 1959).

Another theory which has enjoyed wide popularity is that of Sayers, et al. (Sayers, G. A., Sayers, M., 1945-1946), which holds that the excretion of ACTH depends only on the amount of corticoids in the peripheral blood. When the amount of corticoids in the blood increases, the excretion of ACTH from the pituitary decreases, while the decrease of adrenal steroids in the blood causes an increase in the production of ACTH (Sayers and Sayers, 1947, 1948; Afinogenova 1957; Yudayev, 1961; Mayorova, 1963; Shapiro, et al., 1958).

However, not even this theory can explain all of the experimental data. In the first place, it has been shown that the level of corticoids in the blood is not the only factor governing the secretion of ACTH. Thus, for example, in adrenalectomized animals with a high ACTH level in the blood, the action of a "stressor" leads to further increases in ACTH in the blood. In the second place, it has been established that the pituitary plays an important role in the regulation of ACTH secretion. The action of a "stressor" does not lead to excretion of ACTH in animals with a damaged pituitary (Bagramyan, 1964a).

The theory of hypothalamic control of ACTH secretion is widely accepted at the present time (Harris, 1948). The rapid inclusion of the pituitary in a reaction to a stimulus indicates nervous regulation of the activity of this gland. Stimulation of the pituitary by an electric current increases the content of 17-oxycorticosteroids in the peripheral blood (Mason, 1956, 1958).

The link between the hypothalamus and the pituitary is formed by neurosecretion.

The hypothalamus excretes an active agent of peptide type, which has been called the factor which activates the secretion of ACTH: the corticotropin-realizing factor — CRF (Saffran, et al., 1955; Guillemin, et al., 1957; Schally, et al., 1958; Clayton, et al., 1957; Vladmirov, 1963).

The function of the hypothalamus is in turn dependent on the effects of other portions of the central nervous system. Stimulation of the hippocampus, the anterior cingular region and the brain septum inhibits the hypophyseal-adrenal system, while stimulation of the amygdaloid nuclei and the posterior orbital surface stimulates this system (Okinka, 1961; Fendler, et al., 1961; Mason, 1959; Martin, et al., 1958; Endroczi, Lissak, et al., 1959).

By studying the effect of conditioned reflexes on the excretion of ACTH, I. A. Eskin, et al (1957, 1959) showed that the cerebral cortex is also involved in the regulation of ACTH.

It has also been demonstrated that the system formed by the pituitary and the adrenal cortex is involved in the "anxiety reaction", a reflex action produced by the influence of painful stimuli. This is indicated by the fact that stimulation of the endings of cut sciatic and femoral nerves with an electric current is not accompanied by excretion of ACTH (Mikhaylova, 1955; Eskin, 1957; Balitskiy, Zak, 1959).

We should mention that Selye (1961) was able to evoke a GAS by traumatization of even a denervated extremity, and, therefore, suggested that the "first mediators" of the stressor reaction could be chemical substances formed at the affected point.

Redgate (1960) showed, however, that the concentration of ascorbic acid in the adrenals does not decrease when the hind legs are stimulated with an electric current in rats following cutting of the spinal cord at the level of the second thoracic vertebra, as is the case for normal animals. However, stimulation of the front paws of the animals causes excretion of ACTH from the

pituitary. Proof of this is the decrease in the concentration of ascorbic acid in the adrenals.

Consequently, Selye's opinion, as stated above, is not supported, since the involvement of the pituitary-adrenal cortex system in the "anxiety reaction" occurs only with an intact nervous system.

Our studies were devoted to testing Selye's concept of the "chiasmic resistance". We used adrenalin pulmonary edema as the experimental model.

Development of Pulmonary Edema by the Injection of "Adaptive Hormones"

Several experimental studies are currently in progress which are devoted to the study of the role of adaptive hormones in the development of pathological processes and in the development of pulmonary edema in particular.

Thus, Prasad (1958) prevented the development of chloropicric pulmonary /82
edema in guinea pigs by repeated injection of ACTH (1 mg per animal) and prednisolone for three days before the experiment and two injections of 2.5 mg each on the day of the experiment. The author explains this inhibitory effect produced by the use of hormones by the normalizing effect on the collagenic tissue of the interalveolar areas.

However, N. P. Smirnov (1955a, b, 1956a-c) successfully used a preliminary injection of cortisone (5 mg per 100 g) and ACTH (5-10 units per 100 g) to retard the development of toxic pulmonary edema in rats, produced by intraperitoneal injection of ammonium chloride, but in only 50% of the cases. A decrease in the activity of hyaluronidase in the lung tissue was observed. The author showed that the injection of cortisone (10 mg per kilogram) reduces the permeability of the vessels, determining this by the method of I. A. Oyvin and K. N. Monakova (1953).

There are also scattered reports of the use of hormones for prevention of adrenalin pulmonary edema. Thus, Henschler and Reich (1959) prevented adrenalin pulmonary edema in an experiment by preliminary injection of prednisolone in a dose of 8 mg per kilogram.

V. P. Antonov (1964) observed an opposite result in his experiments. After intramuscular injection of ACTH (3 units per animal) into rats four hours before injection of toxic doses of adrenalin (0.5 mg per 100 g, in the chest cavity), the author found severe pulmonary edema in all cases, with characteristic clinical, pathoanatomical and histological symptoms.

Hence, regardless of the large number of studies of the effect of cortical steroids and ACTH on the course of various types of experimental pulmonary edema, the question of the possibility of preventing the development of pulmonary edema remains open.

In order to test the concept of Selye, it is necessary first of all to answer the question of whether adaptive hormones play a role in the prevention of adrenalin pulmonary edema with the action of supplementary stimuli. With this goal in mind, we initially studied the effect of preliminary injection of the usual doses of hormones (ACTH, hydrocortisone and adrenalin) and "physiological" doses of ACTH on the development of adrenalin pulmonary edema and also investigated the development of pulmonary edema under the influence of supplementary stimuli upon the organism with exclusion of the pituitary-adrenal cortex system.

The experiments were performed on 20 white mice of both sexes; 1-2 mg of hydrocortisone were injected intramuscularly 1 to 3.5 hours before injection of a toxic dose of adrenalin into the tail vein. The results of the experiments showed that hydrocortisone reduced the intensity of adrenalin pulmonary edema to a very insignificant degree in the experimental mice, as indicated by the high pulmonary coefficient of these animals (23.6 ± 1.56), approximately /83
equal to the pulmonary coefficient of the control mice (25.6 ± 1.04), which received only adrenalin.

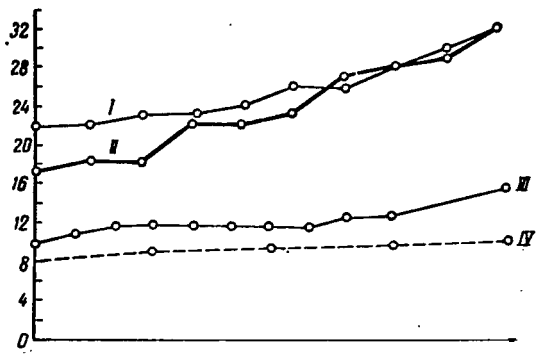

Figure 15. Value of pulmonary coefficient in mice: I - Following injection of adrenalin (10 mice all died); II - After injection of hydrocortisone and adrenalin (10 mice, 2 survived); III - After injection of turpentine and adrenalin; IV - Without injection of adrenalin (5 mice).

Only two of the ten experimental animals survived, while all of the controls (10) died. In contrast to the hormone, a supplementary stimulus (turpentine) prevented the development of pulmonary edema in all animals. This is shown by the variational curves (Figure 15). The difference between the controls and the experimental animals in regard to both indicators (pulmonary coefficient and survival) was not reliable ($P_1>0.2$; $P_2>0.1$). In subsequent experiments performed on 13 mice, we used one of the classical stimulants of the pituitary-adrenal system ("stressors", according to Selye) — adrenalin. In these experiments the adrenalin was injected twice: initially a small amount of adrenalin (0.009-0.015 mg) was injected subcutaneously; three to nine minutes later (i.e., following an interval of time sufficient for prevention of development of adrenalin pulmonary edema by the injection of turpentine) a toxic dose was injected into the tail vein (0.01500-0.02000 for an animal weighing 18 to 24 grams). It was assumed that endogenic adaptive hormones had accumulated in the organism by the time the toxic dose of adrenalin was injected.

The results of these experiments showed that the preliminary subcutaneous injection of small doses of adrenalin has only an insignificant effect as far as inhibiting the development of adrenalin pulmonary edema is concerned. The value of the pulmonary coefficient in the experimental animals (20.6 ± 1.307) is practically the same as that for the control mice (22.3 ± 1.982), which received only one toxic dose of adrenalin. This is illustrated by the variational curves in Figure 16.

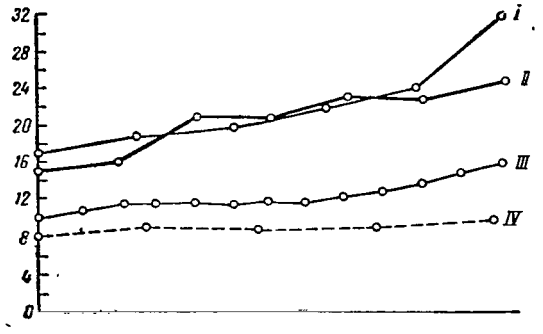

Figure 16. Value of pulmonary coefficient in mice: I - After intravenous injection of toxic doses of adrenalin (6 mice, all died); II - After subcutaneous and intravenous injection of adrenalin (7 mice, 3 survived); III - After injection of turpentine and adrenalin (32 mice, 28 survived); IV - Without injection of adrenalin (5 mice).

Other experiments were performed on rabbits, with small doses of adrenalin being adminstered intravenously. In addition, we increased the time between the injections of the small and toxic doses of adrenalin.

The experiments were conducted on 35 animals with recording of pneumograms and arterial pressure in the right carotid artery. Repeated small doses of adrenalin (0.025-0.005 mg) were injected repeatedly (three to five times) into the marginal vein of the ear. In two experiments, 0.05 mg of adrenalin were injected by infusion in 20 ml of physiological solution. /84

From 20 to 42 minutes after the beginning of the injection of these small doses of adrenalin, a toxic dose of adrenalin was injected into the marginal vein of the ear (0.30-0.35 mg per kilogram, for thirty seconds as usual). In the control experiments, physiological solution was injected instead of the small doses of adrenalin.

The results of the experiments showed that preliminary intravenous injection of small doses of adrenalin had a very slight effect in inhibiting the development of adrenalin pulmonary edema in rabbits, but not in all animals. The pulmonary coefficient in the experimental rabbits was 11.13 ± 0.851 (13.14 ± 0.769 in the controls). The survival of the control rabbits (13 out of 25 survived) and experimentals (5 out of 10 survived) were practically the same (Figure 17). The difference between the experimental animals and the controls was unreliable ($P_1 > 0.1$; $P_2 > 0.5$).

Since, according to Selye, adrenalin is a factor which produces the development of the "stress reaction", we may assume that the "stress reaction",

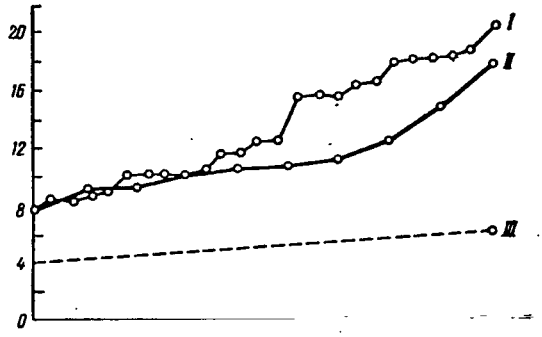

Figure 17. Value of pulmonary coefficient in rabbits: I - After injection of 1 toxic dose of adrenalin (25 animals, 13 survived); II - Following preliminary injection of small doses of adrenalin and subsequent injection of a toxic dose in rabbits (10 rabbits, 5 survived); III - Without injection of adrenalin.

according to Selye, does not play the critical role in this case as far as the prevention of pulmonary edema is concerned.

The slight decrease in the development of pulmonary edema in the experimental animals in the case of preliminary intravenous injection of small doses of adrenalin may be linked not to an increase in the production of adaptive hormones, but to a decrease in arterial pressure. The fact is that a preliminary injection of small doses of adrenalin does raise the blood pressure in the animals, but this increase is insignificant (10 to 15 mm Hg) and brief. In one to three minutes the hydrostatic pressure returned to the initial level as a rule and even decreased somewhat. In the control experiments, however, the pressure was normal (Figures 18-20).

According to Selye, ACTH is a direct stimulator of the production of adaptive hormones; the secretion of ACTH from the pituitary into the blood increases under the influence of any "stressor" on the organism. Hence, in the following experiments which were performed on 31 mice, we attempted to determine whether the development of adrenalin pulmonary edema could be prevented by the timely injection of ACTH. The ACTH was injected intramuscularly in a dose of 2 units per animal; from 2 hours, 53 minutes to 4 hours, 56 minutes later (in different experiments), the usual toxic dose of adrenalin (0.015-0.020 mg per animal) was injected into the tail vein. /85

The results of the experiments showed that preliminary injection ACTH into mice has practically no effect on the course of adrenalin pulmonary edema in them as indicated by the high pulmonary coefficient in the experimental

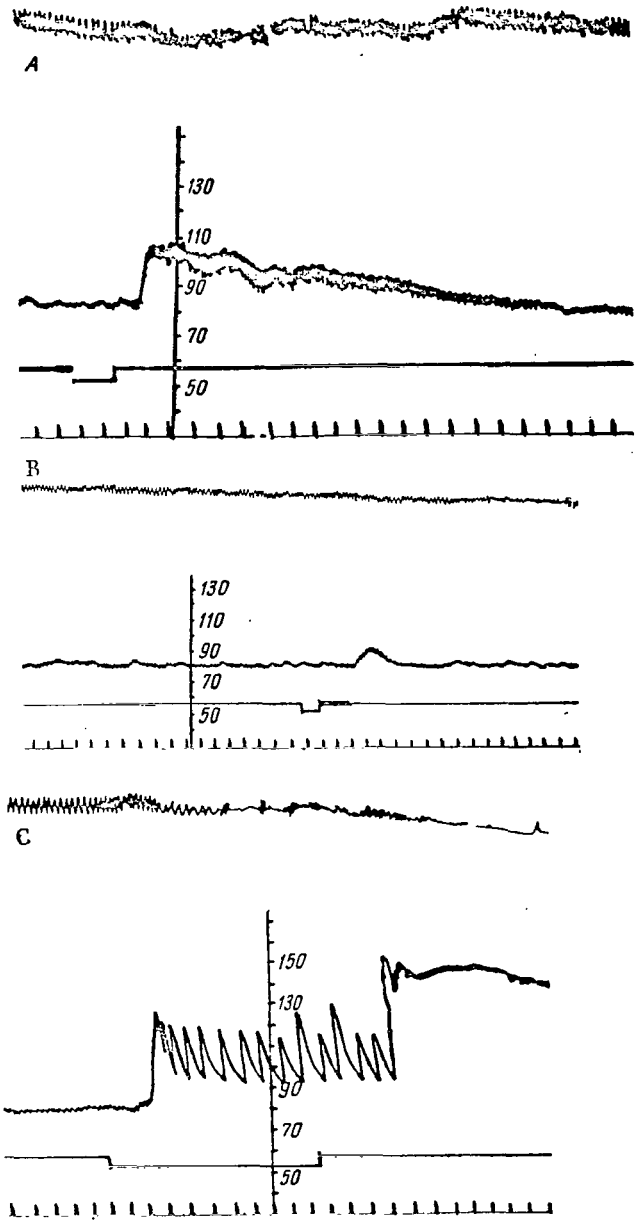

Figure 18. Measurement of arterial pressure (mm Hg in the rabbit, with injection of different doses of adrenalin: A - First injection of a small dose of adrenalin; B - Fourth injection of a small dose of adrenalin; C - Injection of a toxic dose of adrenalin. Curves from top to bottom: respiration, arterial pressure, stimulus mark; time mark — three seconds.

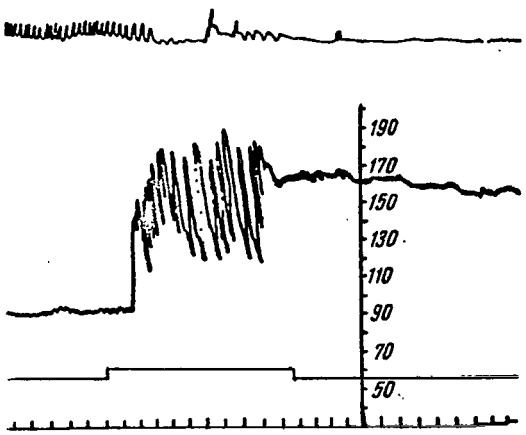

Figure 19. Change in arterial pressure (mm Hg) in an intact rabbit with injection of a toxic dose of adrenalin. Symbols same as in Figure 18.

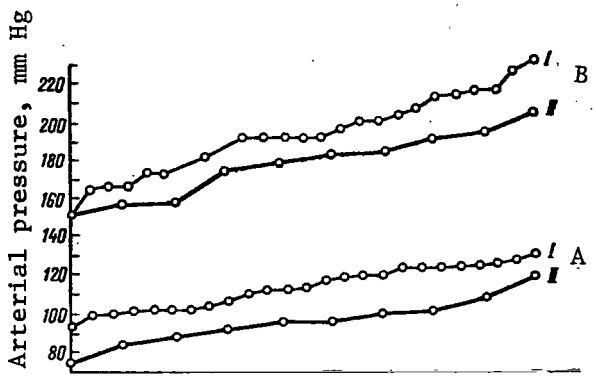

Figure 20. Variational curves reflecting the level of systolic pressure in 25 control rabbits after injection of a toxic dose of adrenalin (I) and in 10 experimental rabbits which received a preliminary treatment with small doses of adrenalin and then a toxic dose (II).

A - Before injection of the toxic dose of adrenalin; B - After injection of the toxic dose of adrenalin.

animals (22.2±1.31), approximately equal to the pulmonary coefficient of the control animals (24.4±1.19), which received only adrenalin. The difference between the experimentals and the controls was not reliable ($P_1>0.2$, $P_2>0.5$). The survival rate for the experimental animals was also only slightly higher: out of 16 experimental mice, only 4 survived (25%), and only 2 out of 15 controls (13.3%). This is illustrated by the variational curves in Figure 21.

Approximately the same result was observed in experiments performed on rabbits to which ACTH was given subcutaneously at the rate of 2 to 12 units per kilogram, 1 to 4.5 hours before intravenous injection of a toxic dose of adrenalin (0.3 mg per kilogram).

The majority of experiments on rabbits involved recording of the arterial pressure and respiration by conventional methods. It is highly significant that the changes in arterial pressure and respiration were the same in rabbits

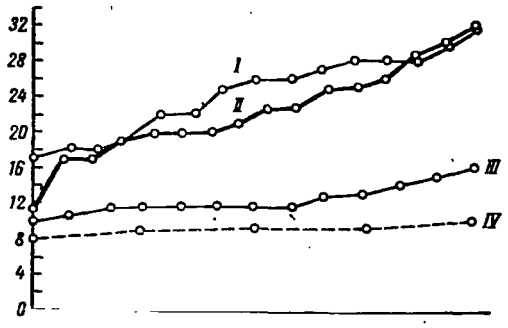

Figure 21. Value of pulmonary coefficient in mice: I - Following injection of adrenalin (15 animals, 2 survived); II - Following injection of ACTH and adrenalin (16 animals, 4 survived); III - Following injection of turpentine and adrenalin; IV - Without injection of adrenalin (5 mice).

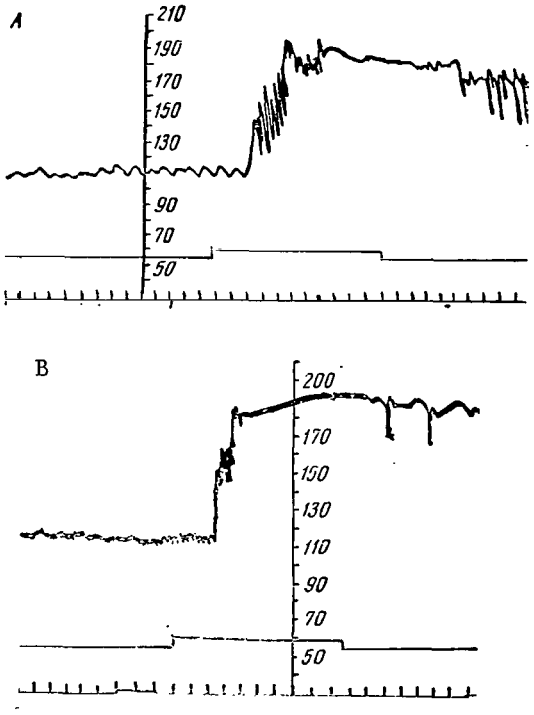

Figure 22. Change in arterial pressure (mm Hg) following injection of a toxic dose of adrenalin: A - In a rabbit which received ACTH; B - In a rabbit which did not receive ACTH. Curves from top to bottom: arterial pressure in the left carotid artery; stimulus mark; time mark - 3 seconds.

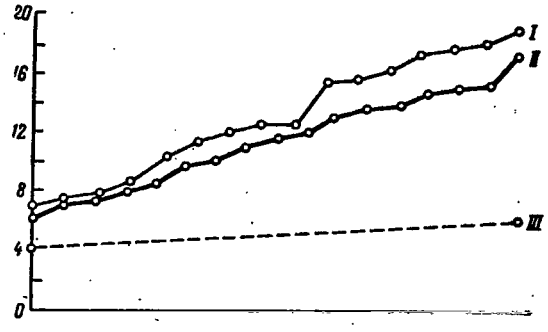

Figure 23. Value of the pulmonary coefficient in rabbits: I - Following injection of adrenalin (16 animals, 7 survived); II - Following injection of ACTH and adrenalin (17 animals, 10 survived); III - Without injection of adrenalin (according to Kan, 1953).

which had received ACTH and in the controls which did not receive ACTH. The results of one of these experiments are shown in Figure 22. Injection of adrenalin into both the control and experimental rabbits raised the arterial pressure to 190 mm Hg. The outcome of the experiment was practically the same for both groups of rabbits: in both cases, severe pulmonary edema developed. /86

/87

The results of all the experiments on 33 rabbits showed that preliminary injection of ACTH has only an insignificant effect in retarding /88 /89 the intensity of development of adrenalin pulmonary edema. The pulmonary coefficient in the experimental (11.3 ± 0.7729) and control (12.9) ±(1.0045) animals was practically the same. The survival rate for the animals was also increased insignificantly; 10 of the experimental rabbits survived (58.8%) and 7 of the 16 controls (43.8%) (Figure 23).

The difference between the experimental animals and the controls was insignificant ($P_1<0.2$; $P_2>0.5$).

The slight decrease in the development of adrenalin pulmonary edema in rabbits following the injection of ACTH may possibly be the consequence of a drop in arterial pressure in these animals. To analyze this theory, we plotted variational curves which reflected the value of arterial pressure in the experimental rabbits, which received ACTH, and the controls, which did not (Figure 24). It is clear from the graph that the arterial pressure at the moment of injection of adrenalin was somewhat lower in the experimental rabbits (which received ACTH) than in the controls (A, II vs. A, I). This regularity was retained even when toxic doses of adrenalin were injected.

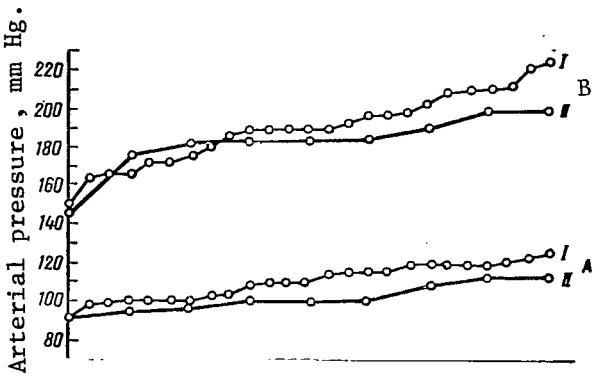

Figure 24. Variational curves reflecting the level of cystolic pressure in 25 control rabbits which did not receive ACTH (I) and in 9 experimental animals which received ACTH (II). A - Before injection of adrenalin; B - After injection of adrenalin.

It is possible in this case, as with the injection of small preliminary doses of adrenalin, that the slight decrease in the development of edema in the experimental animals was the consequence of a slightly lower arterial pressure in these animals. The nature of the curves (especially the upper ones) is definitely reminiscent of the relationship between the variational curves indicating the pulmonary coefficient in the experimental and control animals of this series (Figure 23). /90

Consequently, the preliminary injection of small doses of adrenalin, as well as the use of ACTH and hydrocortisone in doses which are usually used by various investigators for prevention of pulmonary edema, did not produce inhibition of adrenalin pulmonary edema in our experiments similar to that which was observed under the influence of supplementary nonspecific stimuli.

Influence of "Physiological" Doses of ACTH on the Development of Pulmonary Edema

In experiments performed on mice and rabbits, described in the preceding section, we used hormones (ACTH 2 to 10 units per 100 grams) and hydrocortisone, 5 to 10 ml per 100 grams) in doses usually used by other investigators for prevention of pulmonary edema (Antonov, 1964; Cameron and Sheik, 1951; Leytes, Smirnov, 1956b).

However, such doses of hormones obviously cannot have any influence on the organism with a short-term action of a supplementary stimulus. For example, the amount of cortisol in the plasma of the peripheral blood in a

human being, determined under normal conditions by the method of Porter and Zilber, is 15±4.5 micrograms percent, and is still less in rats and rabbits (Berzin, 1964). The ACTH content in human blood plasma is 0 to 32 milliunits per 100 ml (Eskin et al., 1963). According to the data of Mason (1956, 1958) even the direct stimulation of the hypothalamus by an electric current increases the amount of 17-hydrocorticosteroids in the peripheral blood of monkeys only from 24 to 62 micrograms per 100 ml.

It was natural to assume that the brief action of a supplementary stimulus on the experimental animals would produce only a small amount of adaptive hormones. It was very important to determine how these hormonal changes affect the development of pulmonary edema, occurring as they do under the influence of supplementary nonspecific stimuli. In the case of ACTH, this /91 can be done relatively easily, since the increase of this hormone in the blood may be determined by the reduction of the concentration of ascorbic acid in the adrenal glands: the more ACTH is excreted from the pituitary into the blood, the greater the decrease in the concentration of ascorbic acid in the adrenal glands. We performed experiments of this kind on 46 rats.

Determination of the Amount of ACTH in the Blood

This was accomplished by measuring the decrease in the concentration of ascorbic acid in the adrenal glands. Sayers and Sayers 1944-1948) showed that the decrease in the concentration of ascorbic acid in the adrenal glands is proportional to the increase in ACTH in the blood. Using this rule, I. A. Eskin et al.(1963) devised a method of quantitative analysis of ACTH in the blood in man on the basis of the decrease of the ascorbic acid content in the adrenals of rats which had been given an intravenous injection of the serum of the human blood being tested, which contained the amount of ACTH to be determined.

In our experiments, we determined the amount of endogenic ACTH in the blood of rats which had been excreted by their pituitary glands under the influence of a supplementary stimulus on the animal (subcutaneous injection

of formalin) for 30 to 40 minutes. We initially found that during this period of time the content of ascorbic acid in the adrenals decreased on the average by 200 to 200 mg percent (normal value = 430 to 460 mg percent). We then determined how much ACTH is excreted under these conditions from the pituitary into the blood. To do this, we took other rats which had had the endogenic excretion of ACTH blocked (using DOCA) and gave them an amount of ACTH intravenously to reduce the concentration of ascorbic acid in the adrenals of these animals to this value, i.e., 200 to 200 mg% in the 30 to 40 minute period after the injection of ACTH. The content of ascorbic acid in the adrenals was determined by the colorimetric method of Mindlin and Butler (1938). As was shown in a comparative study of several methods of determining the ascorbic acid content in the adrenals (Avad Girgis Avad, 1964) this method is not inferior in accuracy to other more laborious methods.

We repeatedly observed in our experiments that a supplementary stimulus (electric current, formalin, turpentine) did not reduce the intensity of development of adrenalin pulmonary edema to the same extent and under the same conditions in the same kind of animal: in some cases the effect was greater and in some cases it was less.

Proceeding on the basis of Selye's concept of the "chiasmic resistance", we would have to expect that the degree of inhibition of development of pulmonary edema in these experiments would necessarily depend upon the amount of adaptive hormones which were liberated into the blood under the influence of the supplementary stimulus. We tested this hypothesis in special experiments on 19 rats: the animals were immobilized and received as a supplementary stimulus a subcutaneous injection of 0.5 to 0.7 ml of a 4% solution of formalin or 0.3 ml intrapereoneally; 20 to 50 minutes later a toxic dose of adrenalin (0.2 ml per kilogram) was given intravenously. The pulmonary coefficient and ascorbic acid content in the left adrenal were determined in the dead animals. If the animals survived, they were sacrificed by an air embolism in 15 minutes and were subjected to the same examination. /92

The arrangement of the control experiments was the same but without the preliminary injection of formalin.

In eight of the experimental animals, the ascorbic acid content in the adrenals under these conditions, i.e., under the influence of formalin and adrenalin, varied within limits of 153 to 312 ml% (usually 240 to 250 ml%), while in the 11 controls (without the preliminary influence of formalin) it was equal to 191 to 355 ml% (usually 280 to 330 ml%).

Hence, we found that immobilizing the animals for 20 to 50 minutes and injecting adrenalin produced almost the same decrease in ascorbic acid content in the adrenals of rats as the joint effect of adrenalin and a supplementary stimulus preventing the development of pulmonary edema. This means perhaps that both the control animals, which received only adrenalin, and the experimentals, which received both formalin and adrenalin, had about the same increase in ACTH in the blood. However, the pulmonary edema in the control animals was somewhat more serious (pulmonary coefficient 18 to 25) than in the experimentals (8 to 14).

From this we may conclude that the liberation of ACTH into the blood under these experimental conditions did not affect the development of adrenalin pulmonary edema, but the mechanism of the inhibiting effect of a supplementary stimulus on the development of adrenalin pulmonary edema obviously has no relationship to these hormonal changes and takes place by some other pathway.

In the experiments described above, the amount of hormone liberated into the blood remained unknown, and so we attempted to determine the quantitative changes in the ACTH in the blood. I. A. Eskin et al.(1963) developed a rather simple method of quantitative analysis of ACTH in the blood. They showed that the intravenous injection of ACTH (for example, 3.2 milliunits per 100 grams of weight of a rat) produces a drop in the concentration of ascorbic acid in the adrenals by 118 ml%. In our experiments, the supplementary stimulus (formalin) produced a drop in the ACTH concentration by 200 ml%. We may therefore assume that the endogenic ACTH which was released into

the blood of the experimental animals was not 3.2 milliunits per 100 grams of body weight but almost two times that figure. On this basis, we were able to study the influence on the development of adrenalin edema produced by such doses of ACTH, which could be considered physiological. These doses turned out to be almost 1,000 times less than the doses of ACTH which were used by various investigators under similar conditions. We can expect that such physiological doses of ACTH in an experiment will give a clearer answer to the question at hand. /93

With the decrease in the concentration of ascorbic acid in the adrenals, produced by intravenous injection of ACTH, we selected approximately the same amount of that preparation which is released into the blood when formalin is injected, as we determined in previous series of experiments. Still another series of experiments was performed with these doses of ACTH. In this experimental series, we used the conventional method, but instead of employing the supplementary stimulus intravenously, we gave a "physiological" dose of ACTH (3.3 to 12 milliunits per 100 grams of weight in 0.5 ml of physiological solution), followed 15 to 30 minutes later by a toxic dose of adrenalin (0.2 mg per kilogram). As usual, the experiment concluded with a calculation of the pulmonary coefficient as well as the determination of the concentration of ascorbic acid in the left adrenal. In the control experiments 0.5 ml of physiological solution were injected intravenously instead of the ACTH.

The results of the experiments performed on 12 rats are shown in Table 3.

It is obvious from the table that the preliminary intravenous injection of physiological doses of ACTH somewhat increased the intensity of development of adrenalin pulmonary edema in the experimental animals (pulmonary coefficient 20.9 ± 0.804 versus 18.9 ± 1.928 in the controls), but the difference was not significant ($P > 0.5$). The survival rate for the experimental and control rats was the same (two animals out of six survived in each group). /94

These data are illustrated by the variational curves in Figure 25.

TABLE 3. DEVELOPMENT OF PULMONARY EDEMA IN RATS (MALES) WEIGHING 250 TO 300 GRAMS WITH INTRAVENOUS INJECTION OF PHYSIOLOGICAL DOSES OF ACTH AND ADRENALIN AFTER 15 TO 30 MINUTES

EXPERIMENT					
No. of experiment	ACTH, milli-units per 100 grams of body weight	Amount of adrenalin, mg per kilo-gram	Outcome of experi-ment	Pulmo-nary co-efficient	Concentration of ascorbic acid in the adrenals, mg%
359	3.3	0.2	Alive	18.7	238.8
361	3.5	0.2	Dead	22.8	230.0
363	5.0	0.2	"	21.7	240.9
365	7.1	0.2	"	19.2	200.0
367	12.0	0.2	Alive	19.2	200.0
369	7.8	0.2	Dead	23.8	253.0

TABLE 3. (cont'd)

CONTROL				
No. of experiment	Amount of adrenalin, mg per kilo-gram	Outcome of experiment	Pulmonary coefficient	Concentration of ascorbic acid in the adrenals, mg%
358	0.2	Dead	25.5	185.0
360	0.2	"	21.2	238.0
362	0.2	"	20.0	287.0
364	0.2	"	19.5	231.5
366	0.2	Alive	17.2	200.0
368	0.2	"	10.0	241.0

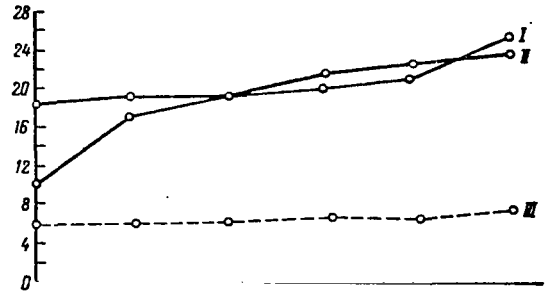

Figure 25. Value of pulmonary coefficient in rats: I - Following injection of adrenalin (6 animals, 2 survived); II - After injection of physiological doses of ACTH (3.3-12 milliunits per 100 grams of weight) and adrenalin (6 animals, 2 survived); III - Without injection of adrenalin.

Hence, we found that the preliminary injection of physiological doses of ACTH (3.3 to 12.0 milliunits per 100 grams of weight) not only did not reduce the development of adrenalin pulmonary edema in the experimental rats, but even intensified the edema somewhat. A comparison of the ascorbic acid content in the adrenals of the control and experimental animals (Table 3) revealed that these values were the same — 200 to 250 mg%. This indicates that the process of immobilization, cutting of the skin and intravenous injection of physiological solution in the control animals stimulated the liberation of approximately the same amounts of endogenic ACTH from the pituitary as the amount of exogenic ACTH which was injected by us into the experimental animals.

Consequently, the experimental conditions (judging by the effect of the ACTH) were the same for both the controls and the experimental animals.

For a definitive answer to the question of the nature of the effect of physiological doses of exogenic ACTH injected into the blood of experimental animals on the development of adrenalin pulmonary edema, it was necessary in setting up these experiments to exclude or prevent the excretion of endogenic ACTH by the pituitary in the animals.

Blockage of ACTH Production

Blockage of ACTH production by the pituitary under the influence of a "stressor" (supplementary stimulus) and the exclusion of the pituitary-adrenal cortex system from the "stress reaction" was accomplished with the aid of DOCA (desoxycorticosterenacetate). In this method, the experiment is

performed on a completely healthy animal, since the mineral and carbohydrate metabolism are not disturbed. The adrenals remain intact, and only the stresses are removed from the reaction. The essence of the method consists /95
in the fact that the mineralocorticoid DOCA, as Avad Girgis Avad and R. N. Shchedrina (1964, 1965) stated, is converted in the organism of the rat into glucocorticoid-corticosterone, which inhibits the excretion of ACTH by the pituitary by a "feedback" mechanism.

The principle of the method is based on the data of Sayers and Sayers (1945, 1947), who showed that adrenal cortical hormones inhibit the production of ACTH by the pituitary, with the degree of this inhibition being proportional to the amount of corticoids introduced from outside.

According to the data of Buttle and Hodges (1953), excretion of ACTH from the pituitary has ceased completely as early as four hours following a single injection of DOCA (15 mg in the peritoneal cavity of a rat) in the presence of such a strong stressor as the surgical removal of one of the adrenals. The completeness of the blockage of the pituitary was evaluated by the authors on the basis of the decrease in the concentration of ascorbic acid in the remaining adrenal (about an hour after removal of the first adrenal). According to the data from the laboratory of I. A. Eskin (Avad Girgis Avad, Shchedrina, 1965, et al.), complete blockage of production of ACTH by the pituitary continues for 16 to 36 hours after the subcutaneous injection of DOCA in amounts of 20 mg per 100 grams of weight for a rat.

This method was used in our experiments as well. The DOCA, dissolved in peach oil and heated to 37 to 38°, was injected in amounts of 20 to 25 mg per 100 grams of body weight beneath the skin of 15 rats.

One day later, the animals were brought back for continuation of the experiments. Nine experimental animals received intravenous injections of ACTH (6 to 60 milliunits per 100 grams each) and a toxic dose of adrenalin (0.2 mg per kilogram) 30 to 60 minutes later. For the others, the arrangement of the experiments was the same as in the preceding series. At the end

of the experiment, we determined the pulmonary coefficient and the content of ascorbic acid in the adrenals in order to evaluate the degree of blockage of the pituitary and to test the correctness of the selected dose of ACTH, the amount of which was chosen so that the concentration of ascorbic acid in the adrenals decreased by 200 to 340 mg% (i.e., to the same degree as under the influence of a supplementary stimulus such as formalin, and for approximately the same period of time). However, the content of ascorbic acid in the adrenals of the controlled rats was 400 to 480 mg%, i.e., these animals developed a pituitary block (the arrangement of the experiments was the same, but physiological solution was injected instead of ACTH). The experiments which did not conform to these requirements were discarded.

The results of the experiments showed that the preliminary injection of physiological doses of ACTH when the pituitary has been blocked by the use of DOCA somewhat increased the intensity of development of adrenalin pulmonary edema in experimental rats, as indicated by the somewhat higher pulmonary coefficient in these animals (16.2 ± 1.056) than in the controls (14.4 ± 1.092), which did not receive ACTH. The survival rate for the experimental animals /96 (8 out of 9 survived) was also somewhat less than for the controls (6 out of 6 survived). However, these differences were not statistically reliable ($P_1 > 0.2$; $P_2 > 0.2$), (Figure 26). Preliminary intravenous injection of physiological doses of ACTH in both intact animals and those in which DOCA was used to exclude the activity of the pituitary did not reduce the development of adrenalin pulmonary edema in rats.

Development of Pulmonary Edema in Animals with the "Pituitary-Adrenal Cortex System" Excluded

In the preceding section we showed that physiological doses of ACTH which are excreted from the pituitary under the influence of the supplementary stimuli which we applied (formalin) have practically no effect as far as reducing the development of adrenalin pulmonary edema in rats is concerned. From this it follows that a supplementary stimulus apparently does not increase the resistance of the experimental animals to toxic doses of

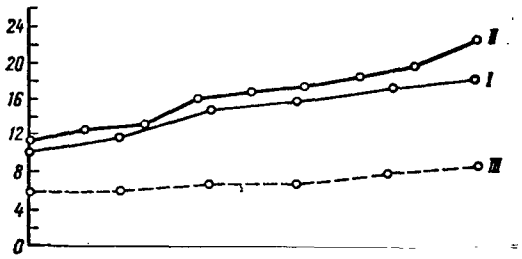

Figure 26. Value of pulmonary coefficient in rats: I - After injection of DOCA and adrenalin (6 animals, 6 survived); II - After injection of DOCA, physiological doses of ACTH (6-60 milliunits per 100 grams) and adrenalin (9 animals, 8 survived); III - In intact animals, which did not receive adrenalin.

adrenalin because of stimulation of the pituitary-adrenal cortex system. However, we can assume that hormonal changes which occur under the influence of a supplementary stimulus have their inhibiting effect on pulmonary edema only in conjunction with the latter. In order to clarify this, we set up three more series of experiments with the usual methodology, the only difference being that in these experiments the animals either had their adrenals removed by operation, or the pituitary was excluded by means of DOCA.

The first series of experiments was performed on 52 white mice. Removal of the adrenals in the acute experiments with mice was accomplished without anesthetic by opening the peritoneal wall. The adrenals were carefully and quickly removed by means of a glass pipette. From one to ten minutes after /97 removal of the adrenals, turpentine was injected subcutaneously (0.2 to 0.3 ml), or into the peritoneal cavity (0.1 ml) and 14 to 17 minutes later a toxic dose of adrenalin (0.020 to 0.030 ml per animal) was injected in the tail vein.

The results of the experiments showed that a supplementary stimulus, both in the animals with the adrenals removed and in those with intact organs, prevents or strongly inhibits the development of adrenalin pulmonary edema. This is indicated by the considerably lower pulmonary coefficient in these animals (17.7 ± 0.69), than in the control animals without use of turpentine (23.3 ± 1.09). The survival rate for the experimental animals (14 out of 23, i.e., 60.9%) was also much higher than for the controls (one out of 21, i.e., 4.76%). The difference between the experimental and control data was reliable ($P_1 < 0.001$; $P_2 < 0.001$).

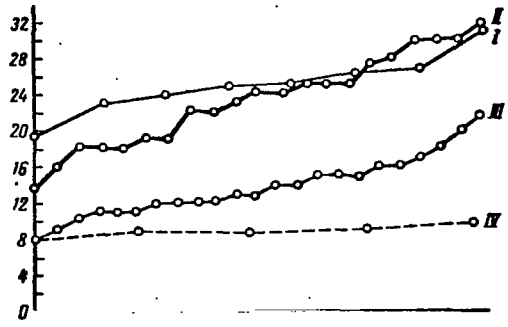

Figure 27. Value of pulmonary coefficient in mice: I - Following injection of adrenalin with intact adrenals (8 mice, all died); II - After removal of adrenals and injection of adrenalin (21 mice, 1 survived); III - After removal of adrenals and injection of turpentine and adrenalin (23 mice, 14 survived); IV - In healthy intact animals.

Adrenalectomy itself somewhat reduced the intensity of development of pulmonary edema caused by the injection of a toxic dose of adrenalin. The pulmonary coefficient for the experimental animals (23.3 ± 1.09) was somewhat less than for mice with intact adrenals (25.0 ± 1.13); all eight mice died. The difference between the groups was not reliable ($P_1 > 0.5$).

These data are illustrated by the variational curves (Figure 27).

Hence, a supplementary stimulus (turpentine) prevents the development of adrenalin pulmonary edema in mice following removal of the adrenals to the same degree as in animals with intact adrenals. Adrenalectomy of itself has an insignificant effect as far as suppressing development of pulmonary edema is concerned.

The principal disadvantage of these experiments was the fact that they /98 were conducted under conditions of acute experiments. Obviously this explains the lower survival rate for the experimental animals under the influence of a supplementary stimulus (60.9% instead of the usual 80 to 90%).

In order to do away with this shortcoming, the following series of experiments on 23 rats with removal of the adrenals was conducted under the conditions of a chronic experiment. Removal of the adrenals in the chronic experiments on rats was performed as a rule under ether or nembutal anesthesia (0.4 ml of a 5% solution of nembutal was injected into the peritoneal cavity), using the widely employed method (through a median dorsal incision in the skin).

The rats recovered rapidly from the operation and lived another six to 17 days on a normal food ration. Instead of water, they received a 1% solution of sodium chloride. From six to nine days after the operation, the state of the animals, as a rule, was good: their behavior was normal, weight remained constant or changed 10 to 15 grams one way or the other, and no fluid was found in the peritoneal cavity when the animals were autopsied after the experiment.

The experiments were performed on all animals in this series six to nine days after the removal of the adrenals. The course of the experiments was the usual: the animal was held down and injected with 0.3 ml of a 4% solution of formalin in the peritoneal cavity or 0.7 ml subcutaneously at four points on the thigh, followed 14 to 40 minutes later by a toxic dose of adrenalin (0.2 ml per kilogram) in the jugular vein.

We initially tried to determine whether or not removal of the adrenals itself has some effect on the adrenalin pulmonary edema. The experiments showed, however, that its level was the same for the experimental animals (pulmonary coefficient 20.6) as for the rats with intact adrenals (pulmonary coefficient 20.6). We then studied the development of pulmonary edema in animals with the adrenals removed under the influence of a supplementary stimulus.

The results of this series not only showed once again that a supplementary stimulus (formalin) considerably decreases the intensity of development of adrenalin pulmonary edema in intact animals, but showed that a supplementary stimulus reduces it in epinephrectomized animals, as indicated by the considerably lower pulmonary coefficient in these animals (11.4 ± 1.4) in comparison to the controls (20.6 ± 1.3). (The arrangement of the control experiments was the same, but without use of formalin.) The difference between the series was reliable ($P_1 < 0.001$).

Of the ten experimental animals, nine survived (90%), but only six of the nine controls (66.7%); the unreliable difference ($P_2 > 0.2$), is obviously

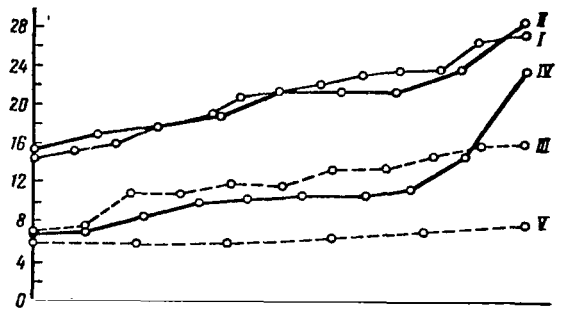

Figure 28. Value of pulmonary coefficient in rats: I - After injection of adrenalin (13 animals, 5 survived); II - After removal of adrenals and injection of adrenalin (9 animals, 6 survived); III - After injection of formalin and adrenalin (11 animals, 11 survived); IV - After removal of adrenals and injection of formalin and adrenalin (10 animals, 9 survived); V - In intact animals, which did not receive adrenalin.

due to the high survival rate of control animals due to the small dose of adrenalin, 0.2 milligrams per kilogram, which is on the border line of toxicity. /99

The supplementary stimulus reduced the intensity of the development of adrenalin pulmonary edema practically to the same extent in the animals with intact adrenals (pulmonary coefficient 12.2±0.4) and the animals with adrenals removed (pulmonary coefficient 11.4±1.4). Four experimental rats in this series received 4% formalin strictly according to Selye's method (1938): 0.5 ml injected three times in 20 hours subcutaneously at equal time intervals. In 20 hours from the start of the action of the "stressor" the usual dose of adrenalin was injected. All of the animals survived and the pulmonary edema (pulmonary coefficient 12-14) was much less than in the controls (pulmonary coefficient 20.6). These data are illustrated by the variational curves in Figure 28.

Hence, the supplementary nonspecific stimulus either strongly reduces or completely prevents the development of adrenalin pulmonary edema both in animals with their adrenals removed and in animals with intact adrenals. Removal of the adrenals of itself does not have any effect on the level of pulmonary edema and even increases somewhat the survival rate of the animals following the injection of a toxic dose of adrenalin.

As we know, exclusion of the pituitary-adrenal cortex system from the stress reaction by means of DOCA is more physiological in comparison to the operational method. Therefore, the last series of experiments was performed

on animals in which production of ACTH was blocked by means of a subcutaneous injection of DOCA, 20 milligrams per 100 grams. In 24 to 27 hours the animals received formalin and adrenalin in the usual manner. Control experiments were conducted with the same method but without injection of formalin. The reliability of the exclusion of the pituitary from the stress reaction was indicated by the high content of ascorbic acid in the adrenals, which was measured after the experiment. The results of the experiments were discarded /100 for ascorbic acid concentrations below 400 mg%. (According to our data, the normal was 400 to 430 mg%, while the data of I. A. Eskin et al.(1963) give 430 to 440 mg%).

The results of experiments performed on 21 rats showed that the supplementary stimulus reduced the intensity of development of adrenalin pulmonary edema in animals in which the pituitary was excluded with the aid of DOCA (pulmonary coefficient 11.7) to approximately the same degree as in animals with intact pituitaries (pulmonary coefficient 15.4). The pulmonary coefficient in the latter case was even somewhat higher.

DOCA of itself had practically no effect on the intensity of development of adrenalin pulmonary edema, as indicated by the pulmonary coefficient of these animals (20.4 ± 2.9), roughly equal to the pulmonary coefficient of rats which did not receive DOCA (19.0). The survival rate of the rats was also nearly the same: of the five rats which received only adrenalin, two survived (40%), while three of the eight rats which received DOCA and adrenalin survived (37.5%) (Figure 29). Consequently, supplementary nonspecific stimuli (formalin and turpentine) prevent the development of adrenalin pulmonary edema both in the case of removal of the adrenals by operation and with exclusion of secretion ACTH by the pituitary with the aid of DOCA.

As we mentioned earlier, according to Selye's concept, supplementary nonspecific stimuli can prevent or inhibit the development of adrenalin pulmonary edema by the production of adaptive hormones. We found, however, that the concept of Selye is of no help to us in explaining the reason for the increase in the resistance under the influence of supplementary

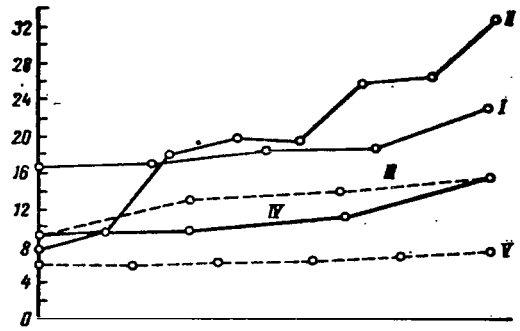

Figure 29. Value of pulmonary coefficient in rats: I - After injection of adrenalin (5 animals, 2 survived); II - After injection of DOCA and adrenalin (8 animals, 3 survived); III - After injection of formalin and adrenalin (4 animals, 4 survived); IV - After injection of DOCA, formalin and adrenalin (4 animals, 3 survived); V - In intact animals without injection of adrenalin.

nonspecific stimuli on the organism. We came to the same conclusions in studying other pathological processes, especially anaphylactoid reactions in rats.

Selye's Concepts and the Anaphylactoid Reaction in Rats /101

Parker and Parker (1924) observed that the parenteral injection of egg white into white rats causes a specific reaction in them which takes the form of dyspnea and sluggishness; the animals lie on their sides. All of this characterizes the state of shock in animals.

In the opinion of the majority of investigators (Parker and Parker, 1924; Selye, 1937-1949; Polushkin, 1958; Ma Bao-li, 1959) this reaction, referred to as anaphylactoid, is similar to an allergic reaction.

We have already mentioned earlier that an important role is played by the nervous system in the development of allergic reactions. We know, for example, that in the experiments of A. N. Bezredok (1928) the anaphylactoid reaction decreases during anesthesia. Guinea pigs did not die of lethal anaphylactoid shock if a resolving dose of serum was given during ether anesthesia. The animals awoke about a half hour after injection of the serum without any after effects. The control animals which received serum without anethesia died of anaphylactic shock. Similar results were observed when using other types of anesthetic (alcohol, ethyl chloride). Urethane and chloralose anesthesia prolonged the lives of the animals, but did not prevent the onset of death.

Prolonged anesthesia, developing following the injection of a mixture of urethane with veronal as well as hypothermy and lumbar novocain block in the majority of cases inhibit or completely prevent the development of such allergic reactions as Schwartzman's phenomenon, Artyus' phenomenon, allergic arthritis (Uchitel' 1950, 1954; Uchitel' and Maysyuk, 1952; Uchitel' and Krymskiy, 1956; Zdorovskiy, 1960).

In one of the series of experiments performed by these authors, using 24 rabbits, an investigation of Schwartzman's phenomenon showed that the control animals (following the resolving injection of an allergen) regularly showed an infiltrate in the form of an induration of the skin with a bluish-red color, 2-3 centimeters in diameter. No macroscopically visible infiltrates were observed in rabbits which were under anethesia during the experiment (Uchitel' and Maysyuk).

P. F. Zdorovskiy, et al (1960, 1961, 1963) suggest that the protective effect from anesthesia, as well as hypothermy and lumbar novocain block, is related to an increase in the production of adaptive hormones. This conclusion is based on the fact that all of these effects (narcosis, hypothermy, novocain block) cause a reduction of the amount of lipoids in adrenal cells which is typical of the state of "stress". This conclusion of the authors agrees with the observations of Ye. V. Stroganova (1956a, b) who found that cortisone dilutes the effect of allergic arthritis and also with the data of Khe Chyu-tszao (1959), who observed a decrease in the resistance of rats to anaphylaxis following removal of the pituitary or the adrenals. However, the preliminary injection of cortisone into the experimental animals (2.5 mg per 100 grams of weight for 7 days) or ACTH one to four units per 100 grams of weight) increases the resistance of rats almost to the level of intact animals. Anaphylactic shock in the white rats in the experiments of Khe Chyu-tszao was produced by sensitizing them with foreign serum mixed with vaseline oil. /102

These data, or more precisely, the results obtained on the basis of these data, agree with the observations of Selye, made as far back as 1937. In studying the different "stressors", the author found that formalin, one of the

strongest "stressors", prevented the development of anaphylactoid reactions in white rats. Selye's experiments were based on 24 female rats, three months old, divided into two equal groups. Each rat in the first group received an intraperitoneal injection of 1 ml. of egg white. From one to three hours after injection, all of the animals showed characteristic edema of the muzzle and tongue, accompanied by hyperemia. A similar edema, but to a lesser degree, appeared in the same animals on the second day when the protein was injected, while on the third day six rats had no edema at all, and on the fourth day none of the rats showed the anaphylactoid reaction.

Every rat in the second group received 0.25 ml of a 4% solution of formalin subcutaneously, followed by 1 ml of egg white interperitoneally. Of the 12 rats in this group, only two developed this form of edema. The author suggests that the resistance of the experimental animals under the influence of the "stressor" (formalin) was increased by excess secretion of anti-inflammatory corticoids. In Selye's opinion, this conclusion is supported by the fact that this inflammatory reaction is sharply intensified in adrenalectomized animals.

The preliminary injection of ACTH or cortisone inhibits the development of anaphylactoid reactions in white rats (Selye, 1949). Hypophysectomy, however, reduces the resistance of these animals to the intravenous injection of egg white by eight to nine times, and adrenalectomy reduces it by 200 times (on the sixth day after the operation). Injection of cortisone reduces the sensitivity of operated animals to normal (Ma Bao-li, 1959).

The majority of these data indicate that the pituitary and the adrenals have a considerable effect on the development of allergic reactions and that the removal of these glands reduces the resistance of the experimental animals, while the injection of ACTH and corticoids restoresthe resistance to normal.

Prolonged and repeated effect of a stressor produces an increase in the /103
resistance of an organism to that "stressor" (direct resistance) and to other

"stressors" (chiasmic resistance) (Selye, 1961b, c). In Selye's opinion, both the "direct" and "chiasmic resistance" are the result of an increased production of adaptive hormones.

However, this conclusion of Selye's must be tested, since neither he nor the authors cited above studied the development of allergic reactions under the influence of "stressors" on adrenalectomized animals, i.e., under the conditions which would exclude the production of adaptive corticosteroids.

We organized such confirming experiments and observed that a supplementary stimulus (formalin) used according to Selye's method (1937) inhibits the development of anaphylactoid reactions in adrenolectomized white rats to the same degree as in intact animals. Moreoever, we found that with repeated injection of egg white the reaction of the experimental animals decreases as it does in the intact animals. We performed our experiments on 67 white rats three months old (females). All of the animals were divided into four groups.

Group One — Control (31 rats). The animals in this group received 1 ml of fresh egg white in the peritoneal cavity. After one to three hours, 23 rats developed an intense edema of the paws, muzzle, tongue and clitoris; in five rats the edema was insignificant, while no edema was found in three. Several hours later, the edema began to decrease, and by the end of the first day (and even earlier), there were no visible traces of edema. After 24 hours, 21 of these rats received a second injection of egg white; the edema described earlier did not appear in the majority of cases. Two animals showed a very slight edema, and the reaction was doubtful in five, while 14 animals showed no edema whatsoever.

Group Two (12 rats). All the animals received an initial injection subcutaneously of 0.25 ml of a 5% solution of formalin; after five to 15 minutes, egg white was injected intraperitoneally. Only one rat developed intensive edema, while three showed insignificant edema and eight animals had no signs whatsoever of anaphylactoid edema.

Group Three (12 rats). The animals in this group had both adrenal glands removed and 10 to 12 days later were injected with egg white in the usual manner. In the majority of cases, the characteristic intensive edema of the tongue, muzzle, paws and clitoris developed in one to three hours. In five rats, the reaction was sharply pronounced; five animals also showed intensive edema, but it was somewhat weaker; only two cases of edema were judged insignificant. The degree of seriousness of the anaphylactoid reaction in the adrenalectomized animals was somewhat greater than in the unoperated rats. Several hours later, the edema began to subside and, by the end of the /104 first day, when the reaction had completely vanished, eight of the animals of this group received a second injection of egg white in the usual manner. In the majority of cases, there was practically no development of anaphylactoid edema. Five rats showed no signs of edema whatsoever, and the reaction in three others was insignificant. On the whole, the anaphylactoid reaction was as insignificant in the adrenalectomized rats upon the second injection of protein as it was in the intact animals, i.e., the resistance of the animals of both groups following the first injection of egg white increased to the same degree.

Group Four (12 rats). These animals also had both adrenal glands removed. After 10 to 12 days, they received 0.25 ml of a 4% solution of formalin, and five to fifteen minutes later each received 1 ml of egg white (intraperitoneally). The results of the experiments showed that the supplementary stimulus (formalin), in the majority of cases, prevented the development of anaphylactoid reactions. In seven cases, there was no characteristic edema; one rat had insignificant edema and four rats had a questionable reaction, i.e., there was practically no edema. The results of these experiments show that a supplementary stimulus increases the resistance of the adrenalectomized rats to the same degree as in the unoperated animals (Figure 30).

Hence, the results of this series of experiments indicate that by acting on the nervous system with a supplementary nonspecific stimulus, it is possible to increase the resistance of adrenalectomized rats to egg white

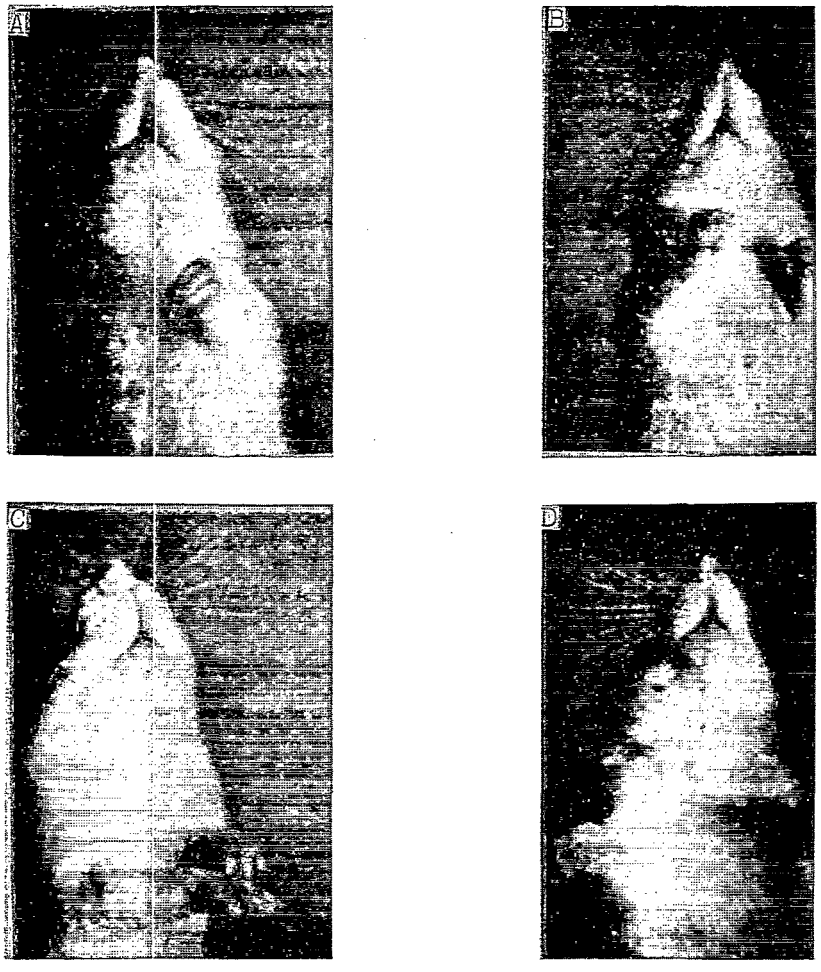

Figure 30. Anaphylactoid reactions three hours after initial intraperitoneal injection of egg white in rats of different groups. A - Intact rat after injection of egg white (edema of muzzle and paws); B - Intact rat after preliminary injection of formalin and injection of egg white (no edema); C - Adrenalectomized rat after injection of egg white (edema of muzzle and paws); D - Adrenalectomized rat after injection of formalin and egg white (no edema).

to the same degree as in intact animals. Moreover, it is apparent from the experiments that the initial injection of egg white increases the resistance of the operated rats to the second effect to the same degree as intact animals, i.e. both the "direct" and "chiasmic" resistance to the foreign

protein developed under conditions which exclude endogenic production of adaptive hormones.

It is necessary to point out that our data on the possibility of increasing the resistance of adrenalectomized animals under the influence of a supplementary nonspecific stimulus do not contradict observations in which it was found that removal of the adrenals reduces the resistance of animals (Khe Chyu-tszao, 1959; Ma Bao-li, 1949). Naturally, when these glands are removed, there is a significant disturbance of metabolism and a significant drop in the ability of the operated to adapt to different conditions. However, the results of experiments which have been conducted indicate that the resistance of the organism can be increased in ways other than by the excretion of adaptive hormones alone, as is suggested by Selye. We must keep in mind, however, that, depending on how the results of experiments on adrenalectomized animals are analyzed, objections may be raised in conjunction with the fact that rats (and mice) sometimes have additional adrenal tissue which can excrete (adaptive) hormones even after the adrenals themselves have been removed. The possibility of such disputes can be excluded only in the event that the experiments are conducted on animals of /106
pure strains which do not have additional adrenal tissue.

We know, however, that all of the initial experiments of Selye, whose results form the basis of the concept of "stress", were also performed on experimental animals in which removal of the adrenals was always considered to be the effect which excluded the "stress" type reaction. Aside from this fact, however, the information obtained in the series of experiments described above indicates that the prevention of adrenalin pulmonary edema under the influence of supplementary nonspecific stimuli did not occur as a result of development of stress type reactions. The facts are the following:

1) The supplementary stimuli prevented the development of adrenalin pulmonary edema, not only in adrenalectomized animals, but also in those with pharmacological (hormonal) blockage of excretion of ACTH, in which the

"stress" type reaction could not be realized (regardless of the presence or absence of supplementary or additional adrenal tissue);

2) Preliminary injection of different doses of adrenalin, according to Selye, acts as a mediator which triggers the "stress" reaction, but it is not able to prevent subsequent development of adrenalin pulmonary edema.

3) Preliminary injection of different doses of "adaptive" hormones had practically no effect on the development of adrenalin pulmonary edema. Hence, the results of all the series of experiments described above indicate that the inhibition of adrenalin pulmonary edema under the influence of supplementary nonspecific stimuli does not occur as a result of development of the "stress" reaction according to Selye but as a result of the influence of some other factors.

We will now present data which indicate the important role of the nervous system in the increase of the resistance of an organism to the action of supplementary nonspecific stimuli.

The facts presented in this chapter indicate that supplementary nonspecific stimuli do not increase the resistance of the organism by means of increased production of "protective" hormones from the adrenal cortex. Hence, the concept of Selye regarding the mechanisms of the so-called "nonspecific resistance" were not confirmed by us. In this regard, it is necessary to study the reasons for this increase in the resistance of the organism. The results of experiments which were designed for this purpose are presented in the next chapter.

CHAPTER IV

FURTHER STUDIES OF THE CAUSES OF AN INCREASE IN RESISTANCE UNDER THE INFLUENCE OF SUPPLEMENTARY NONSPECIFIC STIMULI

In the preceding chapter we showed that the action of supplementary /107
nonspecific stimuli inhibits the development of toxic pulmonary edema and other pathological processes, but not as the consequence of excretion of adaptive hormones, as Selye believes. Naturally, the question arises as to the nature of this mechanism for inhibition of pathological processes.

We have attempted to answer this question by performing special studies of the mechanism of action of two of the supplementary stimuli used by us: turpentine and electric current.

In approaching the study of the mechanism of action of supplementary nonspecific stimuli on the development of adrenalin pulmonary edema, we considered two possible assumptions: either the influence of the supplementary nonspecific stimulus on the development of adrenalin pulmonary edema is accomplished through the nervous system (Kositskiy, 1954, 1955, 1956b, 1962b) or the inhibition of adrenalin pulmonary edema occurs in those cases because of increased production of adaptive hormones, which takes place under the influence of a stimulus — a "stressor" (Selye, 1937, 1949; Selye, 1960, 1961a, b). As we showed in the preceding chapter, an analysis of the facts we observed did not allow us to support Selye's view. It was therefore necessary to study other possible means of action of turpentine on the development of adrenalin pulmonary edema and, in particular, to determine whether an important aspect of this is the stimulation of receptors and afferent nerve endings by turpentine at the site of injection of this substance or whether

turpentine, in order to prevent edema, must first enter the vascular tree and act on some other systems. To do this, we first had to set up experiments in which the turpentine, stimulating a significant receptor zone, would not enter the general circulation. Hence, we had to select an injection site for the turpentine so as to prevent the penetration of turpentine into the general circulation. A suitable site in this regard for injection of turpentine was the animal's paws.

Inhibition of Pulmonary Edema with Preliminary Subcutaneous Injection of Turpentine /108

In the first series of these experiments, we tested the possibility of preventing adrenalin pulmonary edema by injecting turpentine beneath the skin of the hind foot. We injected 0.1 ml of turpentine into each paw 12-15 minutes prior to injection of a toxic dose of adrenalin (the arrangement of the experiments was conventional, with the exception of the change in the injection site for the turpentine). The experiments were conducted on 64 mice.

The results showed that a supplementary stimulant, injected beneath the skin of the paws, completely prevented or strongly weakened the development of adrenalin pulmonary edema (pulmonary coefficient 12.77 $\pm$ 0.56). Twenty-nine out of the 35 experimental animals survived, while 23 of the 29 control mice died with symptoms of severe pulmonary edema (pulmonary coefficient 21.1 $\pm$ $\pm$ 0.7) (Figure 31).

In the next series of experiments, the penetration of turpentine into the vascular tree was prevented, since it was injected with a micropipette into the trunk of a previously prepared sciatic nerve. A toxic dose of adrenalin was given intravenously 10 to 14 minutes later. Under these conditions, the supplementary stimulus did not inhibit the development of adrenalin pulmonary edema in white mice (Figure 32).

Hence, under conditions which preclude the entry of the supplementary stimulant into the vascular tree, the development of pulmonary edema is not

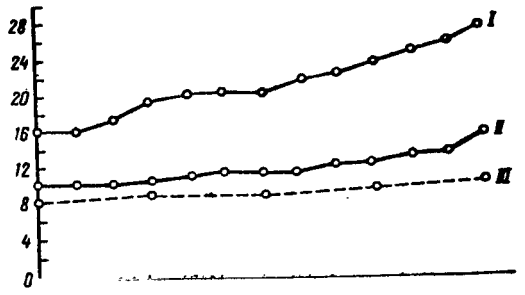

Figure 31. Pulmonary coefficient in mice: I - Following injection of adrenalin; II - Following injection of turpentine subcutaneously in the thigh and adrenalin intravenously; III - In mice without injection of adrenalin.

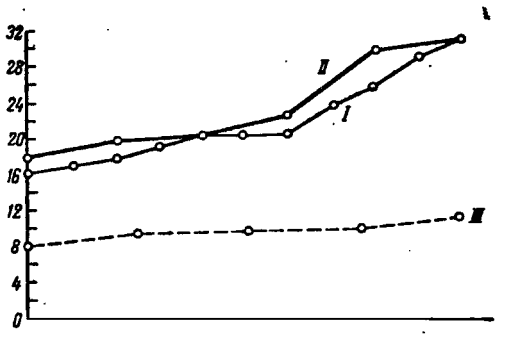

Figure 32. Pulmonary coefficient in mice: I - Following injection of adrenalin (11 mice, 4 survived); II - Following injection of turpentine into the sciatic nerve and adrenalin intravenously (6 mice, 1 survived); III - In intact animals without injection of adrenalin (5 mice).

inhibited. However, the absence of the effect of the absence of the supplementary stimulus may also depend on the fact that turpentine may cause parabiosis of the nerve, preventing the passage of afferent impulses to the central nervous system.

In the next series of experiments, in order to exclude the possibility of a reflex action of turpentine on the vasomotor and other higher centers in 17 white mice, the spinal cord was cut transversely in the region of the lumbar segments. Two to five minutes after cutting the spinal cord, seven mice each received a subcutaneous injection of 0.1 ml of turpentine in both hind legs. Fifteen to 20 minutes after cutting the spinal cord, all of the mice, both the experimentals (i.e., those which had received turpentine) and the controls (which did not receive it), received a toxic dose of adrenalin (0.017-0.036 mg per animal), given intravenously. Two to four minutes later, nine of the 10 control mice died with symptoms of intense pulmonary edema (pulmonary coefficient 22.8 ± 0.91). All seven experimental mice, which

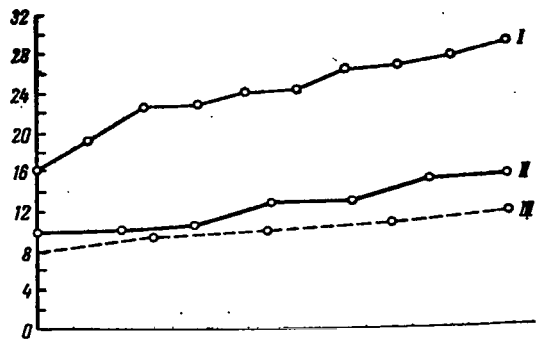

Figure 33. Pulmonary coefficient in mice: I - Following cutting of the spinal cord and injection of adrenalin (10 mice, 1 survived); II - Following cutting of the spinal cord, injection of turpentine and adrenalin (7 mice, 7 survived); III - Without injection of adrenalin (5 mice).

received turpentine, remained alive: there was practically no development of pulmonary edema (pulmonary coefficient 10-12) (Figure 33).

Consequently, after cutting the spinal cord, which prevents the arrival of impulses along the afferent ascending pathways of the spinal cord to the higher sections of the central nervous system, the injection of turpentine prevented or considerably retarded the development of adrenalin pulmonary edema as it did in intact animals. /109

However, cutting the spinal cord is itself a very strong stimulus to the /110 nervous system. It unavoidably leads to spinal shock, not only below the point at which the latter is cut, but (as was shown by E. A. Asratyan (1959), F. A. Oreshchuk (1961) et al.) in the higher sections of the spinal cord, as well, which can lead to disruption of many functions of the organism as a whole.

In addition, there are indications that afferent impulses may travel along the collateral afferent fibers, which are included in the sympathetic trunk.

In view of the above, the next series of experiments on 23 mice involved disconnection of the nervous endings at the site of turpentine injection by infiltration of 0.1 to 0.2 ml of a 2% solution of novocain into the hind paws. Fifteen to 20 minutes later, 0.1 ml of turpentine were injected into 10 mice at the point which had been infiltrated by novocain; all 23 animals then were given adrenalin in the usual manner.

The majority of the control animals (10 out of 13) which did not receive turpentine died two to three minutes after injection of adrenalin showing symptoms of severe pulmonary edema (pulmonary coefficient 21.1 $\pm$ 1.1). The experimental animals which received turpentine after infiltration of the paws with novocain developed much less severe edema (pulmonary coefficient 13.4 $\pm$ 1.22). The difference between the experimental and the control data (on the basis of the value of the pulmonary coefficient) was significant ($P_1 < 0.001$). However, the survival rate for the experimental animals was highly insignificant (4 out of 10 mice survived); this is apparently the result of a general intoxication of the organism, produced by injection of the novocain, turpentine and adrenalin.

It is necessary to mention in this regard that in these experiments the injection of novocain alone also had a somewhat inhibiting effect on the development of pulmonary edema. In intact animals, the same doses of adrenalin produced more severe edema (pulmonary coefficient 23.3 $\pm$ 0.96) than it did in novocainized animals (pulmonary coefficient 21.11 $\pm$ 1.1). Obviously, the novocain reduced the development of pulmonary edema due to its injection into the vascular tree and the partial exclusion of the vascular receptors, so that the adrenalin produced less severe pulmonary edema. The data for these experiments are contained in Figure 34.

For a further study of the possibility of a reflex effect of turpentine, its entry into the vascular tree was prevented by applying tourniquets to the hind paws and cutting off the blood circulation. Turpentine was injected one to two minutes later below the site of application of the tourniquets.

The results of experiments conducted on 28 mice showed that under these conditions the injection of turpentine did not prevent the development of adrenalin pulmonary edema, as indicated by the almost identical pulmonary coefficients for the experimental animals (21.6 $\pm$ 1.37) and the controls (22.5 $\pm$ 0.95) (Figure 35).

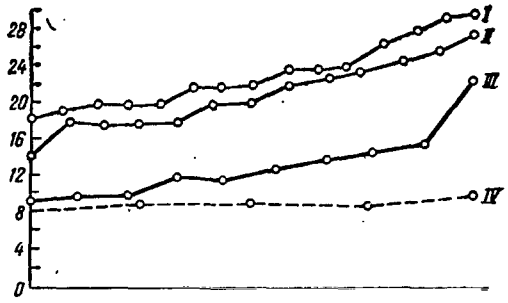

Figure 34. Pulmonary coefficient in mice: I - Following injection of adrenalin (15 animals, 1 survived); II - After injection of novocain and adrenalin (13 animals, 3 survived); III - Following injection of novocain, turpentine and adrenalin (10 animals, 4 survived); IV - Intact mice without injection of adrenalin.

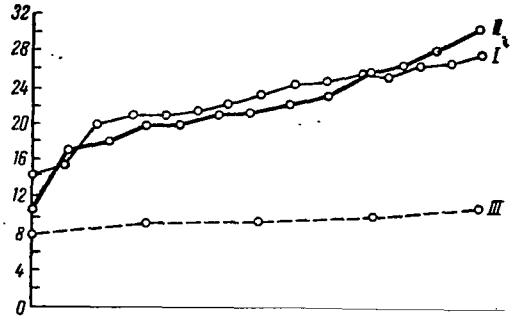

Figure 35. Pulmonary coefficient in mice: I - Following injection of adrenalin (15 animals, 3 survived; II - Following injection of turpentine in the hind paws with application of a tourniquet, cutting off the access of turpentine to the general circulation, and adrenalin intravenously (13 mice, 2 survived); III - Without injection of adrenalin (5 mice).

In these experiments, the tourniquet did not block the passage of nerve impulses, since all forms of sensitivity were retained beneath the point of application of the tourniquet. In special control experiments, it was shown /111 that the application of a tourniquet itself did not cause development of pul- /112 monary edema. Hence, the injection of turpentine subcutaneously in the hind legs under conditions which excluded the passage of turpentine into the general blood circulation did not prevent the development of adrenalin pulmonary edema, while a similar injection of turpentine without preliminary application of a tourniquet prevented the development of edema. Hence, we may conclude that the principal condition for the prevention of the development of pulmonary edema due to the injection of turpentine is the penetration of the latter into the vascular tree.

In the next series of experiments, we limited the time during which the turpentine could enter the vascular tree and distribute itself through the entire organism. This was accomplished by applying a tourniquet after

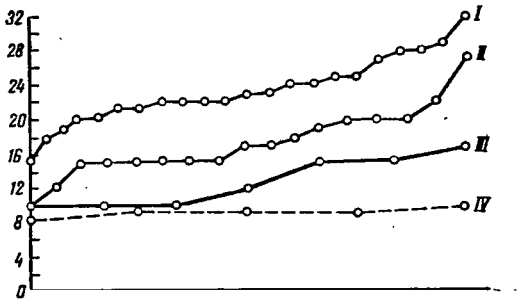

Figure 36. Pulmonary coefficient in mice: I - After injection of adrenalin (22 mice, 1 survived); II - After injection of turpentine, application of a tourniquet (after 5 to 30 seconds) and injection of adrenalin after 9 to 10 minutes (17 animals, 3 survived); III - After injection of turpentine, application of a tourniquet (after 3 minutes) and injection of adrenalin after 9 to 10 minutes (7 mice , 7 survived); IV - Intact animals without injection of adrenalin.

injecting the turpentine. The time from the moment of injection of the turpentine to the application of the tourniquet was varied from five seconds to three minutes. The adrenalin was injected as usual 10 to 15 minutes after injection of the turpentine.

The results of the experiments conducted on 46 white mice showed that in all cases the supplementary stimulus considerably reduced the development of pulmonary edema (Figure 36). This is indicated by the comparatively low pulmonary coefficient of the experimental mice (12 to 18; 20 to 18 in the controls). There was a marked increase in the survival rate for the experimental animals: 21 out of 24 mice survived (76.5%), while only one mouse out of 22 survived in the control group (4.6%). It is interesting to note that when the tourniquet was applied 5 - 30 seconds after injection of turpentine the effect of the action of the supplementary stimulus was less pronounced than when the tourniquet was applied three minutes after the beginning of action of the supplementary stimulus. This is indicative of the fact that the preliminary development of pulmonary edema by the action of turpentine apparently develops not as a result of a stimulation of the paw receptors at the site of injection of the turpentine but as the result of the intake and resorptive action of the preparation.

In order to study the predominantly resorptive effect, in the next series of experiments we injected the turpentine intravenously and into the gastrointestinal tract.

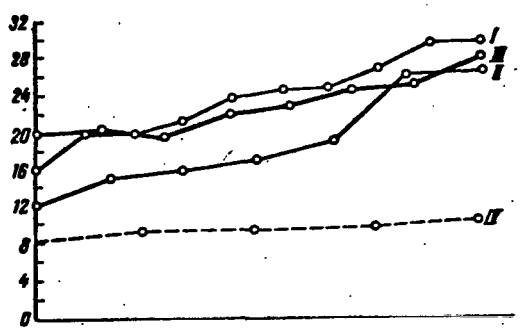

Figure 37. Pulmonary coefficient in mice: I - After injection of adrenalin (10 animals, 2 survived); II - After injection of turpentine intravenously (7 mice, all died); III - After injection of turpentine (1 to 3 drops intravenously) and adrenalin (8 mice, 2 survived); IV - Without injection of turpentine and adrenalin (5 mice).

Study of Pulmonary Edema with Injection of Turpentine into the Veins and Stomach

Intravenous injection of even minimal doses of turpentine (0.0125 to 0.05 ml) caused the development of severe pulmonary edema even without the injection of adrenalin. The pulmonary coefficient of these animals (18.9 ± 2.0) considerably exceeded that for intact animals killed by air embolism (8 to 10).

The intravenous injection of small amounts of turpentine (1 to 3 drops) did not cause death of mice due to "turpentine edema", nor did it inhibit the development of adrenalin pulmonary edema under these conditions (Figure 37). /113

Hence, inhibition of pulmonary edema was observed only under the conditions when the turpentine entered the vascular tree gradually and in small amounts, slowly absorbed from the injection site.

In order to test this conclusion, we organized another group of experiments with the injection of turpentine (0.2 to 0.6 ml) into white mice, into the stomach via a special tube, after which the usual toxic dose of adrenalin was administered intravenously.

The results of these experiments showed that the supplementary stimulus had a much greater effect as far as inhibiting the development of pulmonary edema was concerned if the turpentine was injected in large amounts of 0.5 to 0.6 ml. The pulmonary edema in the experimental animals in this case was much less (pulmonary coefficient 12 to 14) than in the controls (pulmonary

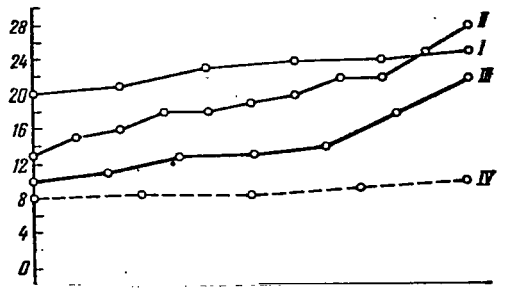

Figure 38. Pulmonary coefficient in mice: I - After injection of adrenalin (6 mice, all died); II - After injection of turpentine (0.2 ml in the stomach) and adrenalin after 15 minutes, 2 hours (11 mice, 8 survived); III - After injection of turpentine (0.5 to 0.6 ml in the stomach) and adrenalin after 9 to 18 minutes (7 animals, 6 survived); IV - Without injection of adrenalin and turpentine.

coefficient 20.5 $\pm$ 0.71). When a smaller amount of turpentine was injuected (0.2 ml), its effect in inhibiting pulmonary edema was weaker (pulmonary coefficient 18 to 20).

However, regardless of the amount of turpentine introduced into the stomach, the survival rate of the experimental animals was high (14 out of 18 survived). All six control mice died (Figure 38). /114

These data, as well as the results of the preceding series of experiments with the injection of turpentine into the paws indicate that the investigated effect of turpentine apparently occurs only in the case of a gradual absorption of the preparation in small amounts into the vascular tree.

How does the preparation inhibit the development of adrenalin pulmonary edema in this case? It is possible that this takes place due to the reduction of blood pressure. However, the injection of turpentine subcutaneously or intramuscularly (in doses which prevent the development of adrenalin pulmonary edema) does not of itself change the level of arterial pressure. We cannot exclude the possibility that the prevention of edema has something to do with the action of turpentine on the permeability of the capillaries of the pulmonary alveoli.

Change in Capillary Permeability Under the Influence of Supplementary Nonspecific Stimuli

Our studies were conducted in experiments on white rats using the method of I. A. Oyvin and K. N. Monakova (1953). We injected 0.1 ml of a 1% solution of Trypan blue into the jugular vein, and 0.02 ml of xylol were applied five to seven minutes later to the previously depilated skin of the animals. The permeability of the skin capillaries was then measured on the basis of the rate of appearance of spots of methylene blue at the points where the xylol was applied. This method was used to measure the permeability of the vessels in minutes: the later the spot appeared after application of xylol, the lower the permeability of the capillaries.

Since we described in one of the series of the previous chapter the effect of formalin on the development of pulmonary edema under conditons of blockage of the pituitary with the aid of DOCA, in this series (together with the study of the change in permeability of the skin capillaries after injection of turpentine and formalin), we measured the changes in the permeability of the capillaries after the injection of DOCA, and with the joint action of DOCA and formalin.

We performed a total of 41 experiments on 37 rats (in some cases two experiments were performed on one animal): Seven experiments involved injection of turpentine, five involved injection of formalin, 12 involved DOCA, and six were devoted to a study of injection of DOCA and formalin. In addition, we organized 11 control experiments using 9 intact healthy animals.

In the control experiments, a colored spot on the depilated skin of the animal appeared five to six minutes (5.6 ± 0.5) after application of the xylol.

In the experiments with rats, 20 to 30 minutes after the injection of turpentine (0.2 to 0.4 ml into the thigh muscles or the peritoneal cavity) it was found that the permeability of the skin capillaries in these animals /115

had decreased significantly: the spot on the depilated skin of the animals appeared only 24 to 39 minutes after application of the xylol. In those rats which had subcutaneous injections (0.7 ml of a 4% solution of formalin in four different areas of the thigh) the time for appearance of the colored spot lengthened to 21 to 37 minutes (28.4 ± 2.3).

Twenty-four hours after injection of DOCA (19 to 27 mg per 100 grams; this amount of DOCA was injected for pituitary blockage) the spot appeared in nine experiments after five to seven minutes (it appeared after 12 to 13 minutes in only three cases), i.e., the permeability of the vessels was nearly the same as in the intact animals.

The permeability of the vessels was studied for 24 hours following a similar injection of DOCA and also with the additional injection of formalin (0.3 ml into the peritoneal cavity or 0.5 ml subcutaneously).

The permeability was determined 10 to 30 minutes after injection of formalin. The time for appearance of the spot under these conditions was 15 to 29 minutes, i.e., the same on the average as for the action of formalin alone without injection of DOCA.

Hence, the permeability of skin capillaries both under the influence of turpentine and under the influence of formalin was found to be much less than for intact rats. This effect of supplementary stimuli is retained even after blockage of the pituitary. However, we cannot say whether these supplementary stimuli reduce the permeability of the vessels of the lesser circulation to the same degree, since we did not study directly the permeability of the alveolar capillaries. We can only assume that such an effect could take place, since these supplementary stimuli sharply limit the development of adrenalin pulmonary edema.

We still were not clear as to whether the action of turpentine in inhibiting edema (as well as that of formalin) is the result of the direct action of these substances (through their absorption into the blood) directly

on the endothelium of the alveolar capillaries or the action of these stimulants indirectly through reflex mechanisms regulating hemodynamics and permeability of the vessel in the lesser circulation. To study this problem, we organized experiments with unilateral and bilateral cutting of the vagus nerves, experiments with inactivation of these nerves by cold, with pharmacological blockage of the efferent endings of the vagus nerves, as well as the ganglia of the vegetative nervous system.

Effect of Inactivation of the Vagus Nerves on the Development of Pulmonary Edema Under the Influence of Turpentine

We know that the principal afferent pulmonary nerves are the vagus nerves. Many authors have indicated the important role played by these nerves in the development of adrenalin pulmonary edema (Bykov et al., 1943a, b; Kam, 1953; Kravchenko, 1955, 1959a-c; Wright, Whitten, 1953).

We can assume that turpentine, after it is absorbed into the blood, has /116 an inhibiting effect on the development of edema through the pulmonary branches of the vagus nerves. Therefore, the following experiments were organized to use animals in which the vagus nerves had been disconnected.

Exclusion of the vagus nerves was accomplished by cutting or cooling them. With the animal fixed in a supine position, a longitudinal incision was made in the skin of the neck (without using anesthesia) and the nerve was prepared carefully on one side with a blunt glass hook (using a binocular loupe). A ligature was applied to the prepared nerve and quickly cut with the sharp edge of a safety razor blade. In the experiments with bilateral vagotomy, the same operation was performed with the second nerve. However, the outcome of the experiments under these conditions may be affected not only by the removal of the nerves but also by additional stimulation of nerves in cutting them.

In order to exclude the stimulation of the nerves when cutting them, in one series of experiments the vagus nerves were inactivated by cold. The prepared nerves were placed on polyethylene tubes through which a coolant was flowing, composed of melting ice mixed with sodium chloride. After several minutes, a cold block developed to prevent passage of impulses along the nerves, indicated by a slowdown of respiration. The blockage of stimuli along the nerves was indicated by the disappearance of the impulsation recorded in the nerves prior to their cooling.

In the first series of these experiments, conducted on 27 mice, the vagus nerves were cut unilaterally (on the right or left side). Five to seven minutes later, turpentine was injected (0.15 ml) into the peritoneal cavity, after which adrenalin was given in the usual manner.

The results of the experiments showed that the supplementary stimulus, even under the conditions of unilateral vagotomy, as a rule prevented the development of adrenalin pulmonary edema (pulmonary coefficient 10.8 ± 1.09): seven out of ten mice survived, while in the control experiments (the arrangement of the experiments was the same with the exception of the fact that the additional stimulus was not employed) all nine mice died with symptoms of severe pulmonary edema (pulmonary coefficient 21.7 ± 1.66). The difference between the experimental and control data was significant ($P_1 < 0.001$; $P_2 < 0.001$).

Cutting one of the vagus nerves itself produced a slight increase in the development of edema in comparison to the control experiments (with intact vagus nerves) (pulmonary coefficient 20.25 ± 0.72). The intensity of edema with unilateral vagotomy was the same in both lungs (Figure 39).

In the next series of experiments, performed on 88 white mice, we studied the development of pulmonary edema under the influence of a supplementary stimulus in animals with bilateral vagotomy.

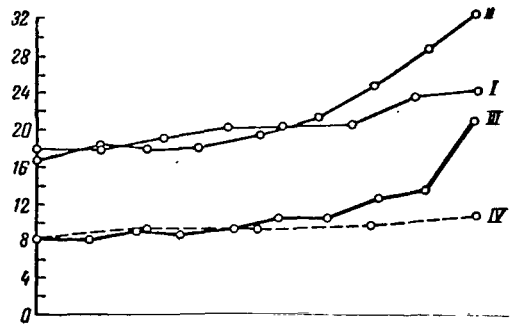

Figure 39. Pulmonary coefficient in mice: I - After injection of adrenalin with intact vagus nerves (8 animals, 1 survived); II - After unilateral vagotomy and injection of adrenalin (9 animals, all died); III - After unilateral vagotomy and injection of turpentine and adrenalin (10 animals, 7 survived); IV - Intact animals without injection of adrenalin.

The arrangement of the experiments /117 was the same as in the preceding series, the only difference being that now both vagus nerves were cut. Each animal received intraperitoneal injections of 0.1 to 0.5 ml of turpentine, 7 to 10 minutes after vagotomy, and adrenalin was injected into the tail vein 12 to 14 minutes after the turpentine. In several experiments the turpentine was injected first and then vagotomy was performed (this had no effect on the outcome of the experiments). In some of the experiments, instead of cutting the nerves we cocainized them with subsequent tight ligation. Since the outcome of all the experiments was the same, we will describe them jointly.

The results showed that injection of turpentine into the peritoneal cavity with both vagus nerves cut inhibited the development of pulmonary edema to a lesser extent than usual (pulmonary coefficient 18.6 $\pm$ 1.01). The survival rate of the mice was also low: only 2 out of 30 experimental animals survived, while 28 died, with about half the cases showing signs of intense pulmonary edema. Out of 18 control mice (the arrangement of the experiments was the same, except that the supplementary stimulus was not employed) 17 died of pulmonary edema whose intensity was somewhat higher than in the experimental animals (pulmonary coefficient 22.4 $\pm$ 1.13). The difference between the results of the groups of experiments, judging by the value of the pulmonary coefficient, was significant ($P_1 < 0.001$), and not significant as far as survival was concerned ($P_2 > 0.1$). In contrast to this, with the vagus nerves intact, a supplementary stimulus in all cases significantly inhibited the development of edema (pulmonary coefficient 13.7 $\pm$ 0.9). All 9 experimental mice survived, while in the control experiments (in which only

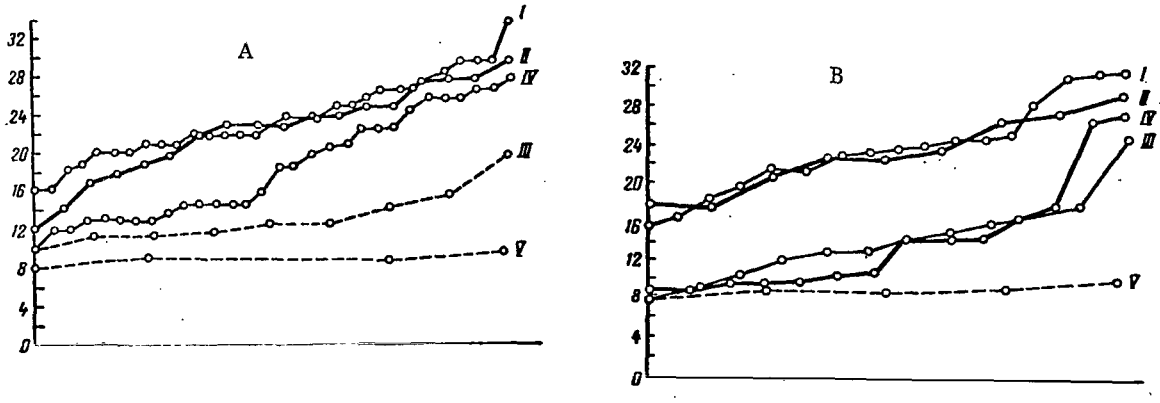

Figure 40. A - Pulmonary coefficient in mice: I - After injection of adrenalin in intact vagus nerves (31 mice, 1 survived); II - After bilateral vagotomy and injection of adrenalin (18 animals, 1 survived); III - After injection of turpentine and adrenalin in intact vagus nerves (9 animals, 9 survived); IV - After bilateral vagotomy, injection of turpentine and adrenalin (30 mice, 2 survived); V - Intact animals without injection of adrenalin (5 mice).

B - Pulmonary coefficient in rats: I - After injection of adrenalin in intact vagus nerves (17 animals, 2 survived); II - After bilateral vagotomy and injection of adrenalin (9 animals, all died); III - After injection of turpentine and adrenalin in intact vagus nerves (12 rats, 9 survived); IV - After bilateral vagotomy, injection of turpentine and adrenalin (14 animals, 7 survived); V - Intact animals without injection of adrenalin.

adrenalin was given) all animals developed severe pulmonary edema (pulmonary coefficient 23.7 $\pm$ 0.77), and only 1 animal out of 31 mice survived.

It is necessary to mention that cutting both vagus nerves of itself has practically no influence on the course of adrenalin pulmonary edema, with edema under these conditions in only a few cases insignificantly weaker in comparison to the animals without vagotomy.

The variational curves of these series of experiments are shown in /118 Figure 40, A.

Hence, the preliminary injection of turpentine with bilateral vagotomy did not have its usual inhibiting effect on the development of adrenalin

pulmonary edema, and the intensity of the edema decreased only in 50% of the cases. There was a high mortality among the animals (92.6%), with the mice dying at the usual intervals, i.e., two to three minutes after injection of adrenalin. We can therefore assume that in order to have an inhibiting effect of turpentine on the development of pulmonary edema the vagus nerves must be intact.

However, the results of experiments performed on rats showed a significant difference with respect to those described above: the supplementary stimulus prevented the development of adrenalin pulmonary edema in rats following bilateral vagotomy to the same degree as in control animals with intact vagus nerves. However, the survival rate for the experimental rats was lower than for the controls, i.e., cutting of the vagus nerves reduced the effectiveness of the protective action of the turpentine. Out of 12 control rats, only 9 (75%) survived, and 7 out of 14 experimentals (50%). Consequently, the resistance in these animals under the influence of a supplementary stimulus and under the conditions of bilateral vagotomy was increased to a lesser degree than in rats with intact nerves (see Figure 40, B). The different degree of effectiveness of the protective effect of the supplementary stimulus in these series of experiments can obviously be explained by the difference in the types of the experimental animals. Cutting the vagus nerves by itself is a strong stimulus which could affect the results of experiments in preceding series.

For this reason, in the next series of experiments the vagus nerves were excluded by means of a cold block to prevent stimulation when cutting them. However, the arrangement of the experiments was similar to the preceding series in other respects.

In experiments performed on 11 mice, we were struck primarily by the fact that the exclusion of the vagus nerves by cooling had a marked effect in inhibiting the development of adrenalin pulmonary edema by itself. The pulmonary coefficient in these animals was much less (18.0 ± 1.76) than in

Figure 41. Pulmonary coefficient in mice: I - After injection of adrenalin with intact vagus nerves (31 mice, 1 survived); II - After cold bilateral "vagotomy" and injection of adrenalin (6 mice, all died); III - After injection of turpentine and adrenalin with intact vagus nerves (9 mice, 9 survived); IV - After cold bilateral "vagotomy", injection of turpentine and adrenalin (5 mice, 1 survived); V - Intact animals.

the purely control experiments (23.7 ± ± 0.77) in which adrenalin was given with intact nerves.

The effect of a supplementary stimulus against a background of a cold block produced only a slight additional decrease in the development of edema (pulmonary coefficient 15.4 ± 1.56). The survival rate of the experimental animals under the conditions of action of turpentine with a cold block on the vagus nerves also increased insignificantly: out of 5 mice, only 1 survived; out of 6 control animals, which did not receive turpentine, all 6 died (Figure 41). /119 /120

Hence, a supplementary stimulus with a cold exclusion, as in the case of cutting the vagus nerves, proved to be much less effective than with intact nerves; the majority of animals died, with a significant number perishing from pulmonary edema.

It must be mentioned that against the background of blockage of the vagus nerves, with the action of a supplementary stimulus and without it, pulmonary edema developed much more slowly in response to the injection of adrenalin and was less pronounced than in intact animals. However, the experimental animals died in both cases, although at much later times (4, 5 or 10 minutes later; the mice usually died from such doses of adrenalin 2 to 3 minutes following injection of the preparation).

Cutting of the vagus nerves disconnects both the afferent and efferent fibers. In this regard, the following series of experiments constitute an

attempt on our part to cut off the efferent synapses. In experiments on 21 mice, 14 animals received 0.25 ml of 0.1% atropine in the tail vein, and 7 of these received 0.1 ml of turpentine in the peritoneal cavity 5 to 9 minutes later. Fourteen to 20 minutes after the injection of atropine, all 14 mice received adrenalin in the usual manner.

The results of the experiment showed that the supplementary stimulus, even under the conditions of atropinization, almost completely prevented the development of adrenalin pulmonary edema, as indicated by the low pulmonary coefficient (11.7 ± 0.5). All seven experimental mice survived, while all seven controls (the arrangement of the experiments was the same, except that the supplementary stimulus was not used) died with symptoms of intense pulmonary edema (pulmonary coefficient 25.6 ± 4.4).

It is necessary to mention that atropinization of itself produced a slight /121 increase in the development of adrenalin pulmonary edema, as indicated by the higher pulmonary coefficient (22.5 ± 4.4) in these mice in comparison with the pulmonary coefficient for animals (21.9 ± 2.8) which received only adrenalin. However, the difference is not significant ($P_1 > 0.2$). All 7 mice which received only adrenalin died two to four minutes later; the 7 atropinized mice also died, but after much shorter times (1 to 2 minutes after injection of adrenalin).

These findings are illustrated in Figure 42.

Hence, a supplementary stimulus (turpentine), under conditions of atropinization of the animals (i.e., with exclusion of the M-cholinoreactive systems in the synapses of the efferent endings of the vagus nerves), inhibits the development of adrenalin pulmonary edema to the same degree as in animals which have not received atropine. Since total exclusion of the vagus nerves (afferent and efferent fibers) reduces the effect of the action of the turpentine, although to different degrees in animals of different types, we can expect that the protective effect of turpentine is obviously accomplished through the afferent fibers of the vagus nerves.

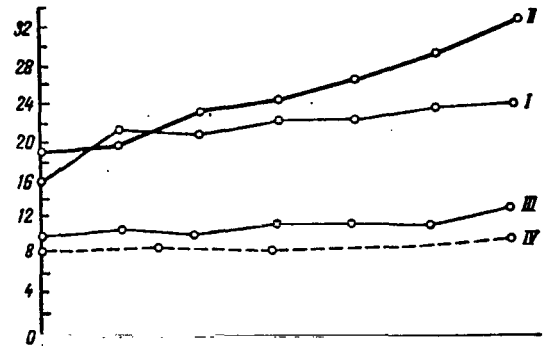

Figure 42. Pulmonary coefficient in mice: I - After injection of adrenalin (7 mice, all died); II - After injection of atropine and adrenalin (7 mice, all died); III - After injection of atropine, turpentine and adrenalin (7 animals, 7 survived); IV - Intact animals.

In the next series of experiments we studied the influence of a supplementary stimulus (injection of turpentine into the peritoneal cavity) on the development of pulmonary edema under conditions of simultaneous exclusion of the N-cholinoreactive systems of the synapses of the vegetative ganglia by the injection of a gangliolytic (pachycarpine) in the M-cholineoreactive systems of synapses of the efferent endings of the vagus nerves by the injection of atropine. The arrangement of the experiments was the same /122 as in the preceding series, the only difference being that the animals simultaneously received atropine and pachycarpine (0.125 $\pm$ 0.25 ml of 0.1% solution per mouse), and then turpentine and adrenalin were given in the usual manner.

These experiments showed that a supplementary stimulus under these conditions prevented the development of adrenalin pulmonary edema, as indicated by the low pulmonary coefficient (12.6 $\pm$ 1.2) in the experimental animals; seven animals out of eight survived (87.5%). All eight control animals (the arrangement of the experiments was the same, except that the supplementary stimulus was not used) died with symptoms of severe pulmonary edema (pulmonary coefficient 22.9 $\pm$ 0.5).

These data are illustrated by the variational curves in Figure 43.

The results of these experiments showed that inhibition of adrenalin pulmonary edema arises only under the condition of penetration of turpentine from the point of its injection into the vascular tree, with the effect being more pronounced with normally functioning afferent fibers of the vagus nerves.

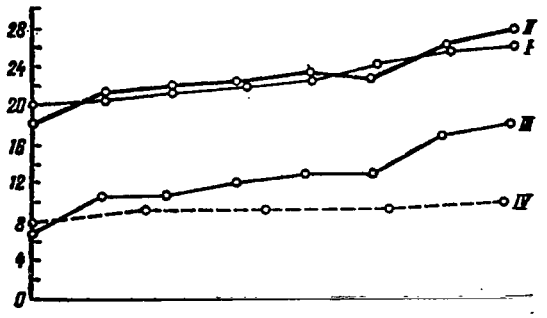

Figure 43. Pulmonary coefficient in mice: I - After injection of adrenalin (8 animals, all died); II - After injection of atropine with pachycarpine and adrenalin after 8 to 15 minutes (8 animals, all died); III - After injection of atropine with pachycarpine, turpentine and adrenalin (8 mice, 7 survived); IV - Intact animals.

In this case, penetration of turpentine causes some kind of rearrangement of the organism in which the adrenalin pulmonary edema cannot develop. It is interesting to note that the resistance of the organism to "edemogenic" action of the adrenalin then increases by tens of times.

In one series of experiments, against the background of action of a supplementary stimulus (0.1 - 0.05 ml of turpentine administrated intraperitoneally) large doses (1.5 - 2 lethal doses) of adrenalin were given. Under these conditions in the experiments, the supplementary stimulus also prevented the development of pulmonary edema. The pulmonary coefficient in these animals was low (10 to 13), and 5 to 6 experimental mice survived. Five control mice died, showing symptoms of severe pulmonary edema (pulmonary coefficient 24 to 28). /123

It was also found that even when 2, 5, 10 or 32 lethal doses of adrenalin were given against a background of action of a supplementary stimulus pulmonary edema did not develop (pulmonary coefficient 9 to 12). Although these mice (10) died as a rule, death occurred at much later times (10 to 20 minutes later) after injection of adrenalin, while the control animals which received only adrenalin died 2 to 3 minutes later. With injection of 48 to 64 lethal doses of adrenalin (against a background of action of a supplementary stimulus) the experimental animals died after the same periods of time as the controls (2 to 3 minutes), but pulmonary edema practically was not to be found even in these cases (pulmonary coefficient 12 to 14) (5 experiments).

The sharp increase in resistance to the "edemogenic" effect of adrenalin is not related to the excretion of "protective hormones" by the adrenal cortex.

It may therefore be assumed that this important increase in the resistance of animals to the "edemogenic" effect of toxic doses of adrenalin has to do with the fact that the effect of the supplementary stimuli may possibly inhibit the reaction of the cardiovascular system to the injection of adrenalin. This question had to be studied specially.

Supplementary Nonspecific Stimuli and the Reactions of the Cardiovascular System to the Injection of Adrenalin

One of the possible mechanisms for the prevention of the development of adrenalin pulmonary edema under the influence of supplementary stimuli may be the reduction of the original level of arterial pressure or prevention of an increase in the latter, usually arising after the injection of toxic doses of adrenalin.

To test this assumption, we performed 77 experiments on rabbits and rats to examine the influence of supplementary stimuli (formalin and electric current) on reactions of the cardiovascular system which arise following the intravenous injection of toxic doses of adrenalin.

Here are some excerpts from the protocols of these experiments.

In control experiment No. 423, without using a supplementary stimulus, injection of adrenalin (0.3 mg per kilogram - 0.025%) resulted in a rise in the arterial pressure of rats from an original level 130 to 135 mm Hg by 60 millimeters, reaching 190 mm Hg. It then fell. At the end of the 6th minute, /124 the pressure began to fall catastrophically, and the animal died showing symptoms of severe incipient pulmonary edema. The pulmonary coefficient (27.4) of the dead rats significantly exceeded the pulmonary coefficient of intact, healthy rats (6-8).

In experiment No. 424, one rat initially received two injections of 0.6 ml or 4% formalin each in the peritoneal cavity, and 24 minutes following the beginning of the action of the formalin a toxic dose of 0.025 adrenalin

(0.3 mg per kilogram) was administered intravenously in the same manner as in control experiment No. 423.

Following the first injection of formalin, the arterial pressure of the experimental rat fell by 5 - 6 mm Hg. (original value — 150 mm Hg) and after several seconds returned to the original level. Seven minutes later, upon the second injection of formalin, the arterial pressure dropped from the original level (140 to 145 mm Hg) by 12 mm Hg; 4 seconds later, its level rose again, and increased further to 163 mm Hg. Three minutes later, however, the pressure again returned to the original value (140 to 145 mm Hg).

After injection of adrenalin, the arterial pressure rose by 65 mm Hg, approximately the same as in the control experiment, reaching a level of 205 mm Hg. Several minutes later, the pressure began to drop and 15 minutes after injection of adrenalin, it stabilized at the original level (143 mm Hg). Twenty minutes after the injection of adrenalin, the rat was killed by an air embolism. Autopsy disclosed that pulmonary edema had developed to a slight extent, indicated by a comparatively low pulmonary coefficient (13.4) only slightly more than the pulmonary coefficient of intact animals (6-8) and much less than in the control experiment (27.4). Similar results were obtained in the other experiments in this series.

Hence, preliminary action of formalin as a supplementary stimulus not only did not change the original level of arterial pressure in the experimental rats, but also failed to have any influence on the degree of increase of blood pressure in the left carotid artery in response to the intravenous injection of toxic doses of adrenalin.

Similar results were obtained when using electric current as the supplementary nonspecific stimulus. When the electric current was switched on, the arterial pressure in the experimental rabbits initially rose by 10 to 30 mm Hg, but rapidly returned to the original level; when the adrenalin was injected, it was the same as before the electric current was applied in the same animals. Often the action of an electric current was accompanied by either a stable

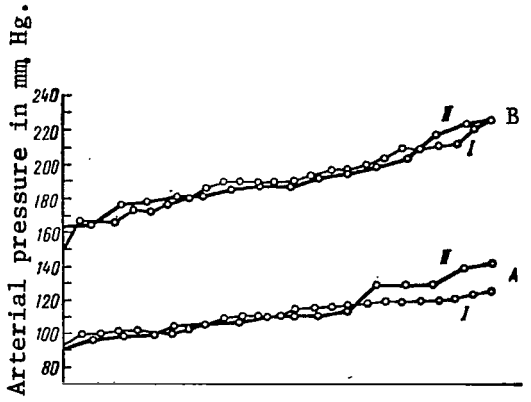

Figure 44. Variational curves showing the level of systolic pressure in 25 control rabbits not subjected to the action of an electric current (I) and in 16 experimental animals subjected to the action of electric current (II). A - Before injection of adrenalin; B - After injection of adrenalin.

reduction or an increase in arterial pressure, but these changes, as a rule, were slight and amounted to only 4-8 mm Hg at the time the adrenalin was injected.

The intravenous injection of /125 toxic doses of adrenalin increased the arterial pressure in the control and experimental animals to approximately the same degree (by 60 to 90 mm Hg).

These results are illustrated by the curves shown in Figure 44.

Hence, the use of electric current and formalin as supplementary nonspecific stimuli of themselves did not change the level of arterial pressure in the greater circulation of experimental animals and had no influence on the increase in arterial pressure produced by the intravenous injection of toxic doses of adrenalin. Nevertheless, the development of pulmonary edema in the experimental animals was inhibited and edema was much less than in the controls.

We cannot exclude the possibility that the supplementary stimuli inhibit the reaction of the vessels of the lesser circulation to the injection of adrenalin and that it is precisely this fact which is the direct cause of inhibition of adrenalin pulmonary edema under these conditions.

To study this problem, we organized experiments to measure the pressure in the right ventricle of the heart with the aid of a sonde and simultaneously record the pressure in the arteries of the greater circulation. The experiments were performed on 19 rabbits of both sexes, weighing 2.5-3.5 kg. We recorded simultaneously the pressure in the right carotid artery and in the

right ventricle of the heart. The systolic pressure in the pulmonary artery was determined on the basis of the level of the systolic pressure in the right ventricle. Recording was accomplished with the aid of electronic manometers on the Mingograph-81. The results from one of these experiments are shown in Figure 45. /126

In this experiment, the blood pressure in the carotid artery and the /127 right ventricle of the heart in the control rabbit (Figure 45, A), which received only adrenalin, were approximately the same as in the experimental rabbit (Figure 45, B and C) which received formalin and adrenalin. In response to the injection of the adrenalin, the blood pressure of the control rabbit as measured in the carotid artery increased to 200 mm Hg, and in the right ventricle to 50 mm Hg, while in the experimental rabbit, it rose to 190 and 50 mm Hg, respectively. Analagous changes were observed in all of the other 19 experiments of this series, whose results indicate that a supplementary stimulus does not reduce the reaction of the systolic pressure to the injection of adrenalin in the vessels of the lesser circulation, but inhibits the development of adrenalin pulmonary edema. Pulmonary edema in the experimental rabbits (which received adrenalin against a background of action of a supplementary stimulus, formalin)was much less (pulmonary coefficient 4-6) than in the controls (pulmonary coefficient 6-12) which received only adrenalin. Seven out of the 8 experimental animals survived and 6 out of the 11 controls (Figure 46).

Hence, the supplementary stimulus considerably reduced the development of arterial pulmonary edema, but did not change the original pressure level in the right ventricle of the heart and, consequently, in the pulmonary artery, and did not prevent its increase when adrenalin was injected. The blood pressure in the right ventricle in both the experimental and control animals was approximately the same, amounting to 20 to 30 mm Hg before injection of adrenalin and 40 to 60 millimeters afterward (Figure 47). The arterial pressure in the greater circulation of the experimental rabbits of this series under the influence of a supplementary stimulus also did not change and was approximately the same as in the control animals (110 to 130 mm Hg).

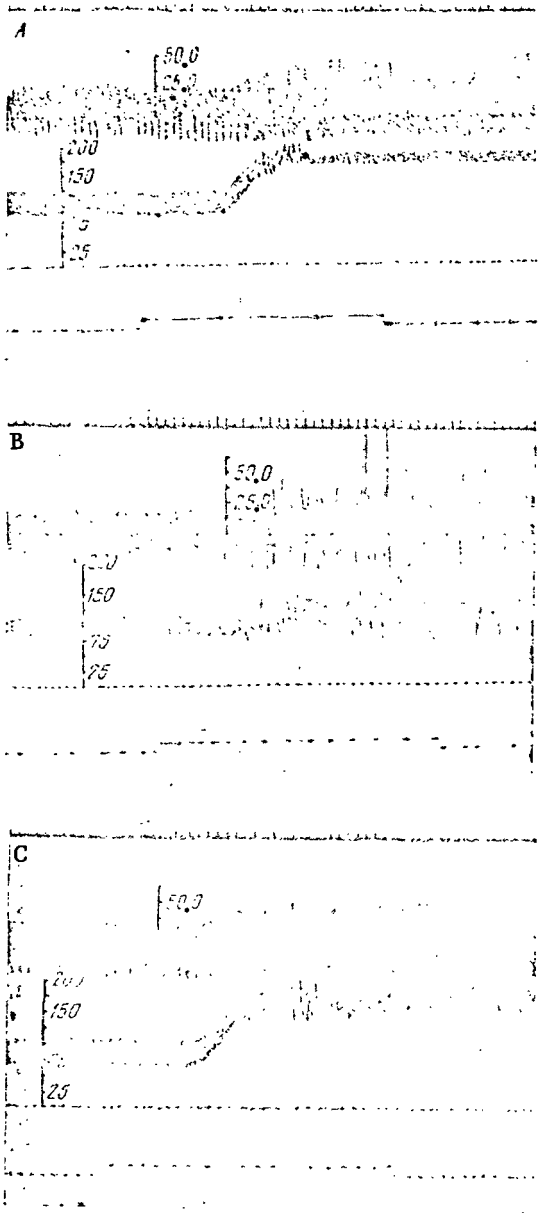

Figure 45. Changes in blood pressure in the right ventricle and the carotid artery in rabbits (in mm Hg).

A - Intravenous injection of a toxic dose of adrenalin in an intact rabbit. The rabbit died of pulmonary edema 13 minutes later. Pulmonary coefficient equals 10.1; B - Intraperitoneal injection of 6 ml of 4% solution of formalin in experimental rabbit; C - Intravenous injection of a toxic dose of adrenalin in the same rabbit 50 minutes after intraperitoneal injection of formalin. Curves from top to bottom: Time marker, 1 second; pressure in the right ventricle; pressure in the carotid artery; zero line for arterial pressure; stimulus marker.

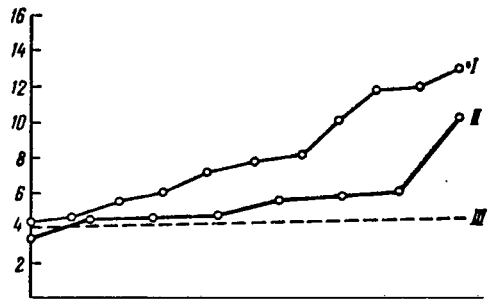

Figure 46. Pulmonary coefficient of rabbits. I - After injection of adrenalin (11 animals, 6 survived); II - Following injection of formalin and adrenalin, after 30 to 40 minutes (8 rabbits, 7 survived); III - Without injection of adrenalin and formalin (after Kan, 1953).

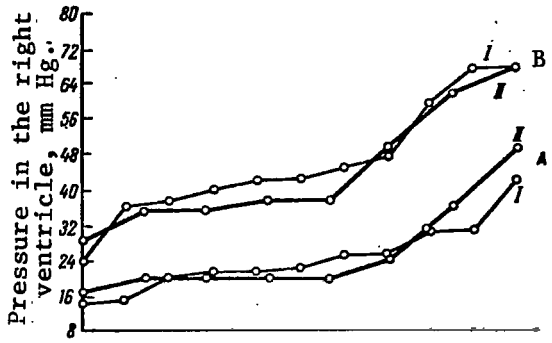

Figure 47. Variational curves reflecting the level of systolic pressure in the right ventricle of the heart in 11 control rabbits which did not receive formalin (I) and 8 experimental rabbits which did receive formalin (II). A - Before injection of adrenalin; B - After injection of adrenalin.

Following injection of adrenalin, the blood pressure in the carotid artery in both groups of rabbits rose by approximately the same value (70 to 90 mm Hg) and reached 220 to 240 mm Hg (Figure 48).

The results of these experiments indicate that the inhibition of the development of adrenalin pulmonary edema by a supplementary nonspecific stimulus apparently does not result from the inhibition of the reaction of the cardiovascular system to the injection of adrenalin.

However, we should mention that the level of the systolic arterial pressure,as we know, does not determine the value of the pressure in the capillaries, on which the development of edema is primarily dependent. We know that a decrease in the tonus of the smooth muscle of the arterioles and precapillaries of the lesser circulation may lead to the opening of the "faucets" of the arterial system and emission of blood from the arteries into the capillaries. It is then possible to have a rise in the capillary pressure

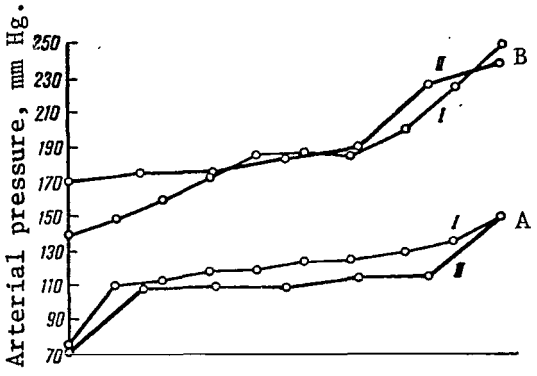

Figure 48. Variational curves showing the level of systolic pressure in the carotid artery in 10 control rabbits which did not receive formalin (I) and in 7 experimental rabbits which did receive formalin (II). A - Before injection of adrenalin; B - After injection of adrenalin.

against a background of a constant (or even reduced) pressure in the arteries. To check this, however, it it necessary to conduct a prolonged /128 continuous recording of pressure in the capillaries of the alveoli with injection of adrenalin and the action of supplementary stimuli, which we were not able to do under our conditions.

In summing up all the series of experiments, it is necessary to emphasize that the influence of supplementary stimuli sharply increases the resistance of the organism of experimental animals to the "edemogenic" effect of toxic doses of adrenalin and to the action of other pathogenic agents. Prevention of edema (judged by the data of the investigation of the blood pressure in the right ventricle of the heart and in the carotid artery) is independent of the inhibiting action of supplementary stimuli on the reaction of the cardiovascular system, which occurs under the conditions of injection of adrenalin.

In the case when the supplementary nonspecific stimulus was turpentine, the increase in resistance did not depend on the local stimulating action of this substance on the tissues, receptors or afferent nerve fibers at the point of injection of the preparation, but was related to the absorption of turpentine from the injection site into the blood stream. A minor role in the increase of resistance is played by the normal function of the afferent systems of the vagus nerve. At the same time, however, the exclusion of the efferent synapses of this nerve did not prevent the increase in the resistance of the organism which occurred under the influence of a supplementary stimulus.

One might expect that the accomplishment of this effect involves the nervous system, at least the afferent fibers of the vagus nerve. What are the efferent pathways and devices (effectors) whose changes in functional state or activity lead to the indicated sharp increase in the resistance of an organism?

At the present time, we still cannot answer this question. Our experiments indicate definitely only that this effect is not realized by increased excretion of "protective hormones" from the adrenal cortex and that it consequently cannot be explained within the framework of the concept developed by Selye.

It is possible that this effect is dependent upon an increased production of some other kind of hormones or substances. It is possible that it is related to factors which we have not been able to investigate directly in experiments: changes in the permeability of the alveolar capillaries, a change in the relationship between the tonus of the smooth muscles of the walls of the arterioles and arteriovenous anastomoses (which can lead to an increase in pressure in the capillaries of the lesser circulation without a significant change in the pressure in the pulmonary artery) or changes in other factors.

It is apparent from the data presented that the mechanisms for increasing the resistance of the organism under the influence of such supplementary nonspecific stimuli as turpentine and formalin is rather complex and many studies will still be required to understand them. /129

Therefore, we attempted to answer at least one (very important, as far as we were concerned) question as to what pathway might be used to accomplish the effect of supplementary stimuli which inhibit pathological processes. Is this effect based on some other still incompletely known humoral mechanisms or is the effect of inhibition of pathological processes in our experiment accomplished through the nervous system? Many facts which were disclosed in our experiments and described earlier tend to favor a nervous rather than a /130

humoral character for the responsible phenomena. The relationship of the effect of inhibition of pathological processes to the sequence of action of nonspecific and pathogenic stimuli: the development of inhibition of a pathological reaction only at a certain strength of the supplementary stimulus, producing characteristic changes of the general behavior of an animal (total stupor, numbness); absence of the inhibiting effect on pulmonary edema in cases when the supplementary stimulus was very strong or, on the other hand, very weak and did not produce a general slowing down of the animal, but instead caused a sharp increase in the motor activity — all of these facts suggest that the principle of dominance is involved in these phenomena. We can assume that the nonspecific stimulus forms a focus of dominant stimulation in the central nervous system, i.e., the conditions under which all subsequent stimuli reinforce this focus of stimulation, losing the ability to evoke the specific reactions characteristic of them. This can involve inhibition of reflex components and the pathological processes which we studied, and can produce inhibition of these processes. To study this problem, we used several features of the nervous and humoral mechanisms of regulation and especially the greater inertia of the humoral mechanisms. We know that exclusion of the stimulus in many cases leads to a rather rapid cessation of reflex reactions. However, the dominant focus of stimulation possesses a certain degree of inertia which allows it to maintain its excitation due to impulses which were "addressed" to other centers. The nerve centers themselves, however, exhibit phenomena of "circular rhythm" so that a stimulus circulates in them even after cessation of influx of the corresponding afferent impulses.

A. A. Ukhtomskiy (1925) showed that only dominance produced by certain humoral or hormonal changes in the organism possesses significant inertia. However, in the case when the cause of development of dominance was the influx of afferent impulses without corresponding receptors, the exclusion of the impulses leads to a rapid liquidation of dominance.

It is precisely these features which were used by us in the further /131
analysis of these phenomena. We proceeded on the basis of the assumption that if the reason for the increase in resistance in the organism is the

development in the central nervous system of a focus of dominant stimulation, due to the action of a supplementary nonspecific stimulus, the exclusion of this stimulus would comparatively rapidly lead to the liquidation of this dominant focus as well (and, consequently, to the disappearance of the increased resistance which had developed in the meantime).

On the other hand, if the reason for the increase in resistance was the accumulation in the blood of certain hormones, the resistance would be retained for a long period of time after the exclusion of the action of the supplementary nonspecific stimulus, since the inactivation and disruption of the hormones circulating in the blood would require a certain period of time, as we know. In this connection, we studied the reactions of the organism to toxic doses of adrenalin for different periods of time after the exclusion of the action of the supplementary nonspecific stimulus.

Development of Adrenalin Pulmonary Edema Following Exclusion of the Action of a Supplementary Nonspecific Stimulus

In a series of experiments performed on 17 mice, the length of action of the supplementary stimulus — a pulsed electric current with a frequency of 42 Hz at a current strength of 4-5 mA (electrodes implanted in the stomach wall and penetrating into the peritoneal cavity) — was 15 to 25 minutes as in the preceding experiment, but the current was switched off 1 to 7 minutes prior to injection of the toxic dose of adrenalin.

Under these experimental conditions, the supplementary stimulus had practically no effect in inhibiting the development of pulmonary edema, as indicated by the almost identical pulmonary coefficient in the experimental animals (20.9 ± 2.0) and controls (22.0 ± 2.0), which were not subjected to the action of the electric current. Out of 10 experimental mice, 5 survived (50%), but only 1 of the controls (14.3%); consequently, the survival rate for the experimental animals was increased rather significantly by 34.7%. However, the difference between the experimental and control data was not reliable ($P_1 > 0.5$; $P_2 > 0.1$).

Hence, when the electric current was shut off 1 to 7 minutes prior to injection of toxic doses of adrenalin, the resistance of the organism relative to a toxic dose of adrenalineincreased to a lesser degree than with the continuous action of a supplementary stimulus. If the reason for the reduction /132
of development of adrenalin pulmonary edema under the influence of a supplementary stimulus were the excretion of some "adaptive" hormones, exclusion of the stimulus 1 or more minutes prior to injection of adrenalin could hardly stop its action, inhibiting the development of edema, since the protective hormones will already have been excreted and would have to be circulating in the blood. The rapid disappearance of resistance due to exclusion of the supplementary stimulus indicates that the nervous mechanism of inhibition of pulmonary edema under the influence of a pulsed electric current is a more likely responsible factor. We came to the same conclusion in experiments in which the supplementary nonspecific stimulus consisted of pulses of current of different frequencies.

We know that not every frequency of electric pulses is able to produce a dominant focus of increased excitability. The optimum frequency for electric current to cause dominance in the spinal cord of the frog is 40 to 80 impulses per minute (Ukhtomskiy, Vinogradov, 1925; Vetyukov, 1926). The delay (or reduction) in the development of adrenalin pulmonary edema in rabbits in our experiments was observed under the influence of an electric current with a frequency of 50 Hz. It is possible that this frequency is also the most favorable one for obtaining dominance in mammals. In this case, the pulses of current with a different frequency did not necessarily cause the development of a focus of dominant excitation. If the reason for the resistance, i.e., the inhibition of pathological processes, were related to the appearance of a focus of dominant excitation, a change in the frequency of the stimulating impulses would cause the resistance to disappear. However, if the resistance were related to the excretion of adaptive hormones, a change in frequency of stimulating impulses would not have any noticeable effect in changing the signs of resistance since the adaptive hormones, according to Selye, are produced under the influence of any "stressor".

In this connection, we organized studies of the development of adrenalin pulmonary edema under the influence of a supplementary stimulus in the form of electric impulses of different frequencies.

Development of Adrenalin Pulmonary Edema Under the Influence of Electric Impulses of Different Frequencies

The first series of experiments was performed on 26 guinea pigs using as the supplementary nonspecific stimulus an electric current with a frequency of 42 Hz (an electronic stimulator made by the Leningrad Experimental Plant) and a frequency of 50 Hz from an induction coil made by the Kiev Medical Apparatus Plant (KMAP) (the primary winding of the coil, passing through a chopper, was connected through a step-down (to 5-4) transformer to the line voltage, which established the stimulating frequency of 50 Hz. /133

A toxic dose of adrenalin (0.15 - 0.30 mg/kg) was injected 15 to 20 minutes after the beginning of action of the supplementary stimulus. In other respects, the nature of the experiments was conventional (electrodes implanted in the stomach wall and penetrating into the peritoneal cavity).

The results of this series of experiments are shown in Table 4.

It is apparent from the table that in the overwhelming majority of cases, turning on the electric current prior to the injection of adrenalin sharply reduced the intensity of development of adrenalin pulmonary edema in the experimental guinea pigs. This is indicated by the considerably lower pulmonary coefficient for these animals (17.4 ± 1.409), than in the controls (25.1 ± 7.721), which received only adrenalin. The survival rate for the experimental guinea pigs was also much higher (11 out of 18 survived, i.e., 61.6%) than for the controls (all 8 died). The difference between the experimental and control data was significant ($P_1 < 0.001$; $P_2 < 0.001$) (Figure 49).

TABLE 4. DEVELOPMENT OF ADRENALIN PULMONARY EDEMA IN GUINEA PIGS UNDER THE INFLUENCE OF ELECTRIC CURRENT AND INTRAVENOUS INJECTION OF ADRENALIN

Experiment					Control			
No. of experiment	Electric current in Hz	Amount of adrenalin, mg/kg	Result of experiment	Pulmonary coefficient	No. of experiment	Amt. of adrenalin, mg/kg	Result of experiment	Pulmonary coefficient
8	50	0.3	Alive	10.5	5	0.3	Dead	22.5
9	50	0.3	Dead	22.6	6	0.3	"	16.1
10	50	0.3	Alive	16.6				
25	50	0.2	"	10.0	23	0.2	"	24.0
27	50	0.2	"	19.7	26	0.18	"	29.8
28	50	0.2	Dead	17.0	29	0.15	"	20.2
31	50	0.15	"	20.0	30	0.15	"	29.8
32	50	0.15	Alive	15.0				
33	50	0.15	"	11.0				
67	42	0.15	Dead	21.5	66	0.15	"	28.0
68	42	0.2	"	30.4				
69	42	0.15	Alive	13.0				
70	42	0.15	Dead	23.0				
72	42	0.15	Alive	13.1	71	0.15	"	30.0
73	42	0.15	Dead	29.0				
74	42	0.15	Alive	15.4				
75	42	0.15	"	10.0				
76	42	0.15	"	15.0				

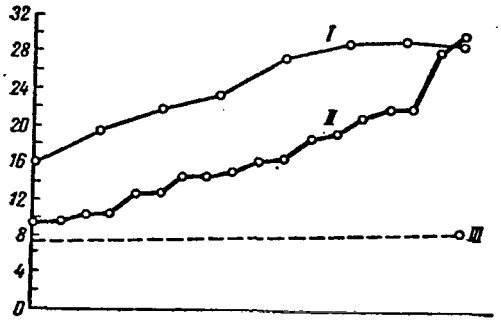

Figure 49. Pulmonary coefficient in guinea pigs: I - Following injection of adrenalin (8 animals, all died); II - After injection of adrenalin with action of electric current, frequency 42-50 Hz (18 animals, 11 survived); III - Intact animals.

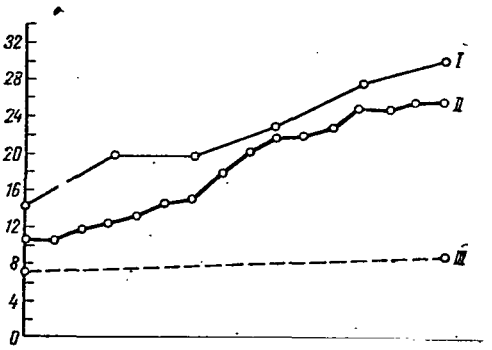

Figure 50. Pulmonary coefficient in guinea pigs: I - After injection of adrenalin, without use of electric current (6 animals, all died); II - After injection of adrenalin with use of electric current, frequency 1/3 - 1/5 Hz (15 animals, 7 survived); III - Intact animals.

Hence, under the influence of an electric current (frequency of 42 to 50 Hz), the development of adrenalin pulmonary edema in guinea pigs was significantly reduced. /134

A second series of experiments was performed on 21 guinea pigs using a pulsed electric current with a frequency of 1/3-1/5 Hz as the supplementary stimulus; the current was supplied by the above-mentioned electronic stimulator. In other respects, the conditions for the experiments were the same as in the preceding series.

The results of this series of experiments showed that the use of widely spaced pulses of electric current as a supplementary stimulus led to a slight increase in the resistance of the organism toward "edemogenic" effects of toxic doses of adrenalin in experimental guinea pigs. This is supported by the rather high pulmonary coefficient in these animals (19.1 ± 1.36), much less than in the controls (22.5 ± 2.09), which were not subjected to the action of the supplementary stimulus. The survival rate of the experimental animals was also less than in the preceding series: seven out 15 guinea pigs

survived (46.7%), while all 6 controls died ($P_2 < 0.01$). These data are illustrated by the variational curves in Figure 50.

These facts favor a "nervous" mechanism for these phenomena. If the increase in resistance were related to the excretion of certain adaptive hormones under the influence of a supplementary stimulus, the increase in resistance would not be related to the difference in the frequency of electric impulses. /135

Hence, the results which we obtained can be used to support the theory that the supplementary nonspecific stimulus produces a focus of dominant excitation in the central nervous system. This leads to inhibition of all other reactions on the part of the organism, including those which arise under the influence of pathogenic stimuli.

If this assumption is valid, supplementary stimuli must produce inhibition, not only of reactions that lead to pulmonary edema, but of any other reflex reactions of the organism; in addition, the degree of inhibition of any reflex reactions would necessarily be correlated to some degree with the degree of inhibition of the adrenalin pulmonary edema. This assumption was also checked in a special series of experiments.

The Effect of Supplementary Nonspecific Stimuli on Certain Reflex Reactions of the Organism

We proceeded on the basis of the assumption that if the action of an electric current (or another nonspecific stimulus) in the central nervous system leads to the formation of a focus of dominant excitation, it must also inhibit other reflex reactions on the part of the organism, including reflex shifts in respiration and blood circulation, which arise under different influences on the organism.

As such influences, we used various stimuli: 1) A jet of air directed at the cornea of the eye; 2) A 1.5% solution of ammonia, applied on a cotton swab to the nostrils of the animal; 3) Introduction of 0.5 ml of 1%

hydrochloric acid into the mouth; 4) Mechanical stimulation of the skin of the thigh; 5) Mild stimulus of the skin of the left thigh with an induced electric current; 6) Compression of the left carotid artery to reduce the pressure in the region of the sino-carotid node; 7) A change in the position of the axis of the body to an angle of 45° to the horizontal with the head down; 8) The same, with the head up; 9) Hypoxia (breathing into a closed rubber balloon with a capacity of 0.25 liters); 10) Stimulation of the mechanoreceptors of the rectum by the inflation of a rubber balloon (pressure of 1.80 mm Hg); 11) Stimulation of the central segment of the left vagus nerve; 12) A jet of air directed into the nose from a 25 ml rubber balloon; 13) A continuous sound stimulus (the noise obtained from tone generator 3G-10) /136 or a sudden stimulus (click).

Such a wide range of completely different stimuli was specially selected to study the possibility of external inhibition of (theoretically all) reflex reactions with the development of a focus of dominant excitation in the central nervous system under our experimental condition.

All of the stimuli listed above were administered strictly in terms of intensity. Their duration of action usually amounted to 30 seconds, with the exclusion of the ammonia (15 seconds) and the hydrochloric acid, which was introduced into the mouth and not washed out; such stimuli as the directed jet of air or the click acted instantaneously.

All 13 of these measured brief active stimuli will be referred to in the future as "tests" (by analogy with the "test stimulus" of N. Ye. Vvedenskiy). The intensity and duration of each "test" stimulus was selected so as to produce pronounced reflex changes in respiration and blood circulation.

The rabbits were immobilized in a supine position in the usual stand. After the experiment had been prepared (application of the systems for recording respiration, arterial pressure in the left carotid artery on a continuously rotating electric kymograph, and insertion of electrodes into the thigh muscles), we studied in sequence the action of 7 to 9 "test"

stimuli. The action of the stimuli was studied 1-3 times in each experiment. The interval between the applications of the different "test" stimuli was 1-2 minutes. Under these conditions, the action of the different test stimuli produced stereotypic, completely uniform effects as far as corresponding effectors were concerned, which affected the arterial pressure and respiration.

After studying the reactions to the "test" stimuli, a supplementary stimulus was applied, which continued to act until the end of the experiment: the induced electric current. Alternating current (50 Hz) at 4 V was applied to the primary winding of the above apparatus, passing through a chopper (which set the stimulating frequency of 50 Hz). The intensity of the stimulus, as usual, was set so that the rabbit was in a state of stupor and numbness (3.5 to 8 cm distance of the windings in the "KMAT" apparatus).

Ten to fifteen minutes after the electric current was switched on, against the background of its activity, the same "test" stimuli were applied repeatedly in the standard sequence. The value of the reflex reactions developed under these conditions were compared with the values of the reactions which were observed in the animals prior to the switching on of the electric current. After this, the usual toxic dose of 0.1% solution of /137
adrenalin (0.3 mg/kg) was injected for 30 seconds into the marginal vein of /138
the ear. The organization of the control experiments in this series was the /139
same, except that the supplementary nonspecific stimulus (electric current) was not included.

All of the surviving animals were killed with an air embolism 15 minutes after injection of the adrenalin.

Prior to the action of the electric current, each of the "test" stimuli produced the usual marked increase in arterial pressure by 15 to 20 mm Hg for 30 to 50 seconds (after which the pressure returned to the original level) and a stoppage of respiration for 10 to 20 seconds in the phase of maximum inspiration, with a subsequent shift of the entire respiration curve upward

due to general muscular tension of the animal. When applying the same "test" stimuli against the background of action of an electric current, the changes in respiration and drug circulation either did not appear at all or were much less than when the same "test" stimuli were used on intact animals (i.e., prior to the turning on of the electric current). This is illustrated by the kymograms for several experiments. Figure 51 shows that stimulation of the respiratory pathways by ammonia in an intact rabbit prior to switching on of the electric current (A, I), raised the arterial pressure by 44 mm Hg. The same stimulus against a background of supplementary stimulation (B, I) raised the arterial pressure by only 15 mm Hg in all, i.e., the reaction was reduced 2.9 times. The changes, as far as respiration are concerned, were about the same in both cases, with the exception of the fact that in the first case the reaction in regard to respiration and arterial pressure was in two phases.

The introduction of a 1% solution of hydrochloric acid into the mouth of this same intact rabbit raised the arterial pressure by 37 mm Hg and caused a general motor reaction, which resulted in oscillating movements of the writing point that recorded the respiration (Figure 51, A, II). However, when this same stimulus was applied during the action of electric current there were no changes in the arterial pressure or respiration (Figure 51, C, II).

This same pronounced inhibiting effect of a supplementary stimulus (electric current) on the reflex changes in respiration and blood circulation was observed in the other experiments as well. Thus, for example, when the /140
cornea of a rabbit's eye was stimulated with a jet of air before the action of the electric current, the arterial pressure increased by 8 mm Hg (Figure 52, A, I.) However, the use of this same "test" stimulus (a jet of air on the cornea of the eye) against the background of activity of an electric current did not cause a change in arterial pressure (Figure 52, A, II).

The injection of 0.5 ml of a 1% solution of hydrochloric acid into the oral cavity of an intact rabbit produced an increase in the arterial pressure by 16 mm Hg (Figure 52, D, I). During the action of this same "test" stimulus

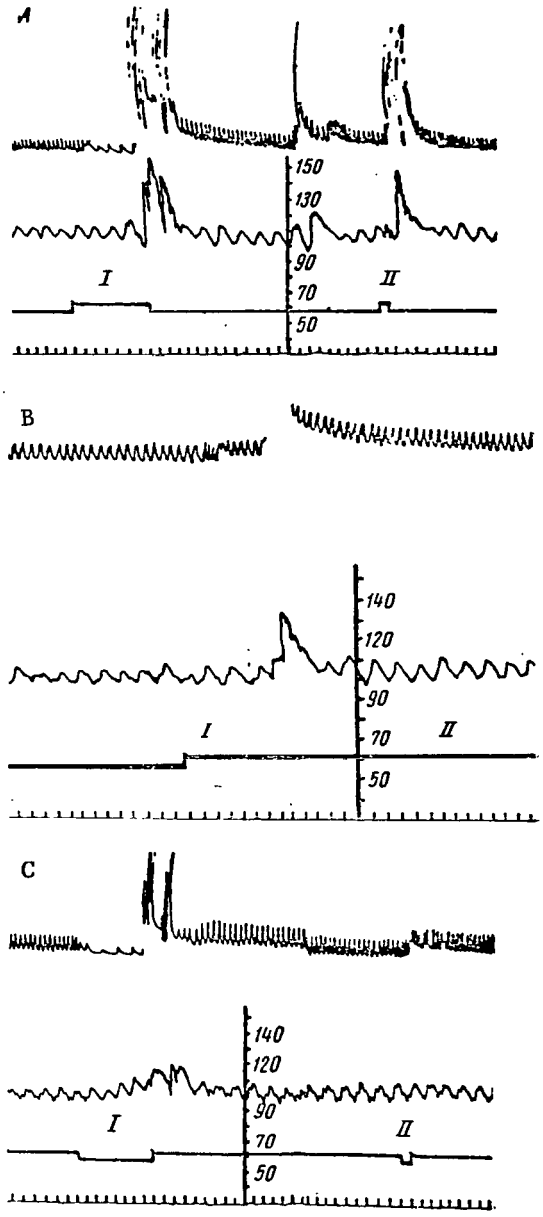

Figure 51. Changes in reactions of a rabbit to inhalation of ammonia vapor and injection of a solution of hydrochloric acid into the mouth with the application of a supplementary stimulus (electric current):

A - Before application of electric current; B - Moment of turning on electric current; C - Against a background of application of electric current; I - Inhalation of ammonia vapor; II - Application of hydrochloric acid to the mouth. Curves from top to bottom: Pneumogram; arterial pressure (mm Hg); stimulus marker, time marker - 2 seconds.

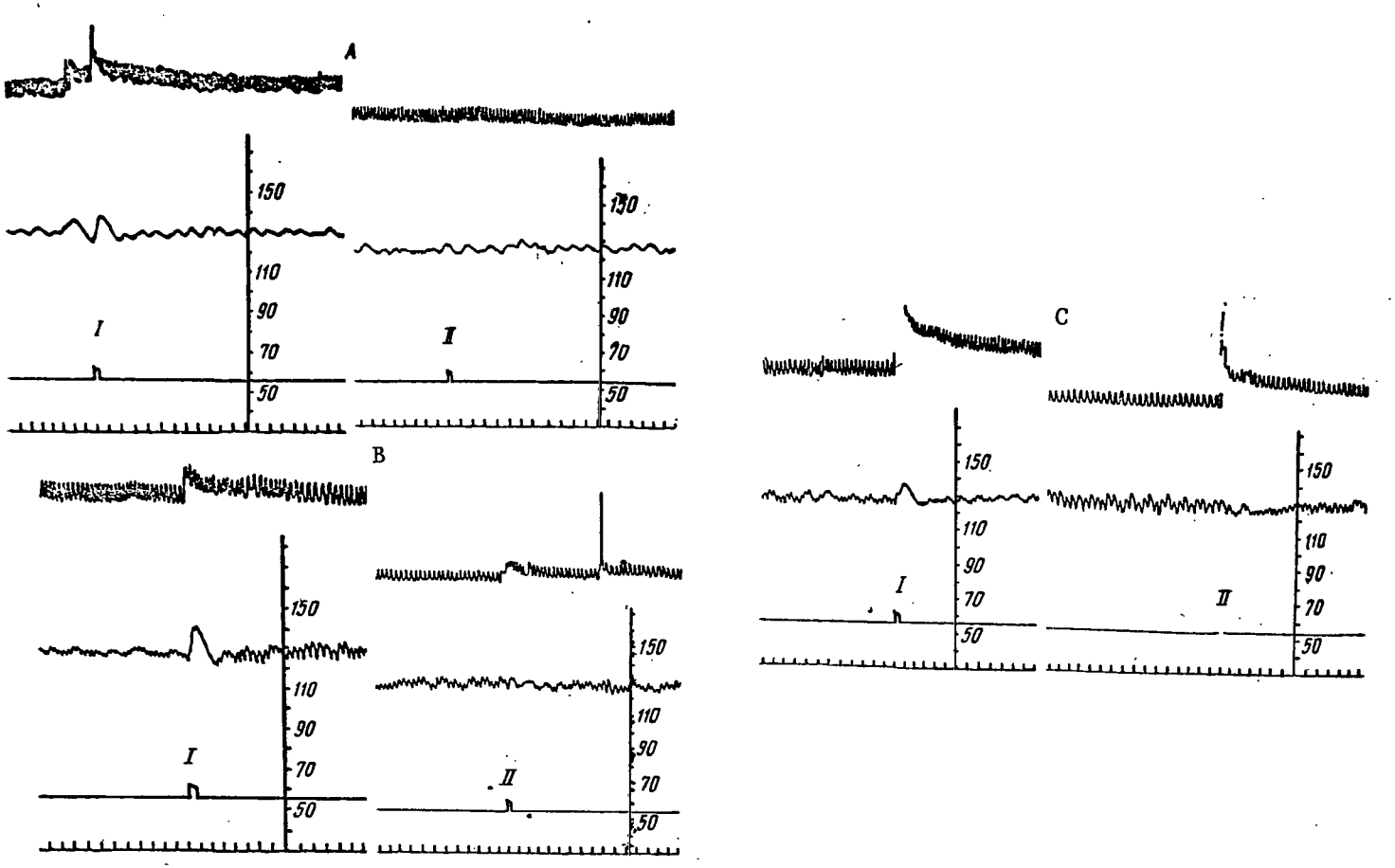

Figure 52. Change in reactions of a rabbit to certain test stimuli during application of an electric current: A - Stimulus of cornea of the eye by a jet of air; B - Application of 0.5 ml of a 1% solution of hydrochloric acid to the mouth; C - Stimulation of the skin of the thigh; I - Before turning on electric current; II - Against a background of application of electric current. Curves from top to bottom: Pneumogram, arterial pressure (mm Hg), stimulus marker, time marker - 2 seconds.

against the background of action of an electric current, there were no changes in the arterial pressure (Figure 52, B, II). A similar relationship was observed during mechanical stimulation of the skin of the thigh. The reflex changes in respiration and general motor reaction of the animal under these conditions against the background of action of electric current were also significantly less than prior to the switching on of the current (Figure 52, c).

Hence, against the background of action of a supplementary stimulus (electric current), the reflex changes in respiration, blood circulation and total motor activity of an animal, produced by different "test" stimuli, are sharply reduced and in some cases completely inhibited. These features were observed in the overwhelming majority of the experiments which we conducted.

Similar observations were made by Hernandez-Peon, Scherrer and Jouvet (1956). They showed that the value of the bioelectric potentials in the cochlear nucleus of the cat in response to standard sound stimuli (clicks of uniform intensity) is sharply reduced in the case when a new dominance develops in the animal (when, for example, the cat finds itself in a new situation, i.e., if new stimuli begin to operate causing a change in the animal's attention and its lively interest).

After applying the "test" stimuli against a background of prolonged activity of a supplementary stimulus (electric current), 16 rabbits received intravenous toxic doses of adrenalin.

The pulmonary edema, as always, in the experimental animals was 2.5 times less against a background of application of an electric current (pulmonary coefficient 8.68 ± 0.53) than in the controls, which were not subjected to the effect of a supplementary stimulus (pulmonary coefficient (13.5 ± 0.77); the difference was statistically reliable ($P_1 < 0.001$).

However, the survival rate was increased insignificantly: out of 16 experimental rabbits, 10 survived (62.5%), while 13 out of 25 controls

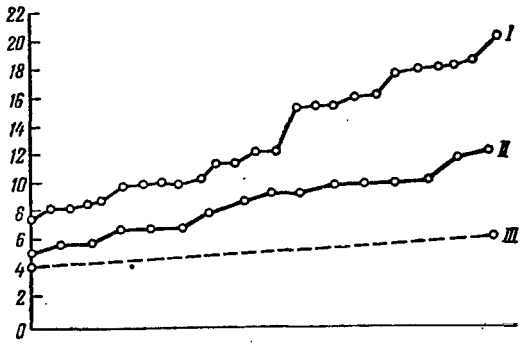

Figure 53. Pulmonary coefficient in rabbits. I - After injection of adrenalin (25 animals, 13 survived); II - After injection of adrenalin with application of electric current (16 rabbits, 10 survived); III - Intact animals without injection of adrenalin (after Kan, 1953).

survived (52%); the difference naturally is not reliable ($P_2 < 0.5$). It is necessary, however, to note that the experimental rabbits lived twice as long (8-9 minutes) after injection of adrenalin as the controls (4-5 minutes).

We have included some variational curves which illustrate these results (Figure 53). /141

Hence, the preliminary application of a supplementary stimulus (electric current) inhibits both the reflex changes in respiration and blood circulation produced by the application of various "test" stimuli and the development of pulmonary edema, caused by the intravenous injection of toxic doses of adrenalin, in these experimental rabbits as well.

The analysis of the results of all thirteen experiments showed that in the overwhelming majority of cases the reflex changes in respiration and blood circulation caused in rabbits by the application of "test" stimuli against the background of action of an electric current were much less than the changes produced in the same rabbits with the same "test" stimuli prior to the application of a supplementary stimulus of electric current.

It was only when 2 "test" stimuli (change in the position of the body and stimulating the receptors of the rectum) were applied that the reflex changes in respiration and blood circulation were usually greater against the background of the action of the electric current.

For the sake of illustrating the above, we have included 2 graphs (Figure 54). It is obvious that in almost all cases the reflex changes in

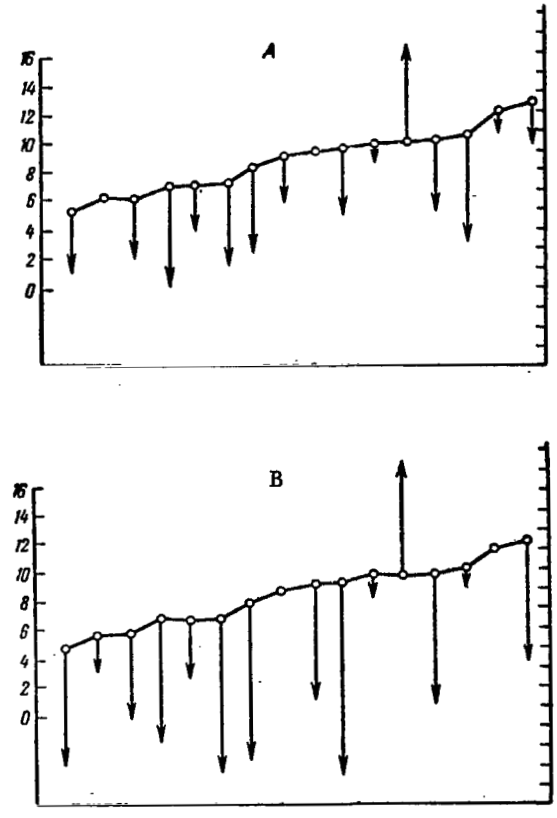

Figure 54. Relationship between the degree of inhibition of reflex changes in respiration and arterial pressure, produced by test stimuli, and the degree of reduction of development of adrenalin pulmonary edema in the same rabbits under conditions of application of electric current.

A - Summary graph reflecting the change in respiration under the influence of all test stimuli; B - Graph reflecting change in respiration under the influence of a single test stimulus, a mild electric current.
The variational curve reflects the value of the pulmonary coefficient in 16 rabbits (the scale of the pulmonary coefficient is at the left). The arrows show the direction and degree of the change in the reflex reactions of respiration to the test stimuli. The length of the arrows reflects the degree of change of reaction under the influence of a supplementary stimulus (in percent relative to the value of the original reaction); one division on the right-hand scale corresponds to a change of 10%.

respiration and blood circulation, produced by "test" stimuli during the action of an electric current were less (arrows directed downward) than before it was applied. In addition, on the left side of all the graphs (i.e., the experiments in which slight pulmonary edema occurred or there was none at all) the arrows are somewhat larger and directed downward more often than on the right hand side of the graph results for experiments in which pulmonary edema was more intensive). This indicates that in experiments with greater inhibition of reflex reactions of the circulatory system and respiration, the development of adrenalin pulmonary edema is inhibited to a greater degree. /142

Hence, a supplementary nonspecific stimulus (electric current) inhibited /143 in experimental rabbits, not only the development of adrenalin pulmonary edema, but reflex reactions of respiration and circulation produced by different "test" stimuli. In some cases it was noted that the more the reflex reactions were inhibited in the experimental animals, the greater the degree to which development of pulmonary edema was decreased in the same animals.

It seems to us that the data obtained support the theory that a supplementary stimulus inhibits the development of adrenalin pulmonary edema, causing a state of dominant excitation in certain points in the central nervous system. However, the development of dominance leads to inhibition of other points and, consequently, to inhibition of other reflex reactions of the organism (including pathological reflexes that lead to the development of edema).

In addition to the facts presented above, this concept is supported by the fact that the supplementary stimulus does not prevent the development of pulmonary edema in cases when it is very strong and produces a sudden motor reaction, i.e., a generalization of the excitation process in the central nervous system. It is interesting to note in this regard that we were unable to use the action of a supplementary nonspecific stimulus to prevent a lethal outcome to the injection of convulsive poisons, especially cordiamine.

We shall present the data from the corresponding series of experiments.

Effect of Toxic Doses of Cordiamine and Supplementary Nonspecific Stimuli

Cordiamine, as we know, has a pronounced stimulating effect on the central nervous system. When it is injected in large doses, it produces clonic and, more rarely, tetanic spasms.

Our experiments were performed on 23 white rats of both sexes weighing 150 to 200 grams. As the supplementary nonspecific stimulus, we used a 4% solution of formalin, which was injected intramuscularly in amounts of 0.2 to 0.4 ml or intraperitoneally 20 to 30 minutes prior to the intravenous injection of a toxic dose of cordiamine (2 ml per kg of the weight of the animal).

The results of the experiments showed that under these conditions a supplementary stimulus does not inhibit the development of pathological processes. All of the animals (the controls which received only cordiamine, and the experimentals, which received formalin and cordiamine) died in spasms approximately at the same time after injection of cordiamine (Table 5). Only one rat, regardless of continuous spasms, survived 23 hours and 30 minutes. We can expect, therefore, that a supplementary stimulus inhibits the development of pathological processes only in the event that it produces a state of inhibition of the central nervous system (the "external inhibition" or "negative induction" according to I. P. Pavlov). However, in those cases when the supplementary stimulus leads to generalization of excitation, or in those cases when the pathogenic agent itself produces generalization of the excitation process in the central nervous system, inhibition of pathological processes cannot be achieved.

These data speak in favor of the concept that the inhibition of pathological processes under the influence of supplementary nonspecific stimuli may be related to the development of a focus of excitation in the central nervous

TABLE 5. DEVELOPMENT OF "CORDIAMINE SHOCK" IN RATS OF BOTH SEXES WEIGHING 150 TO 200 GRAMS WITH INTRAVENOUS INJECTION OF CORDIAMINE AND INTRAPERITONEAL INTRAMUSCULAR INJECTION OF FORMALIN.

Preparation				Control			
No. of experiment	Weight of animal in grams	4% formalin, ml (intraperitoneally	Cordiamine (2 ml per kg, several minutes after the formalin)	Result of experiment (time of death of animal after injection of cordiamine)	No. of experiment	Weight of animal in grams	Injection of cordiamine, ml/kg	Result of experiment (time of death of animal following injection of cordiamine)
37	204	0.5	8 min.	2 min.	30	220	2	9 min.
38	145	0.3	12 min.	13 min.	31	210	2	3 min.
39	260	0.2	11 min.	17 min.	32	260	2	1 hr 51 min
42	155	0.2	20 min.	3 min.	33	195	2	3 min.
43	233	0.4	40 min.	23 hrs 30 min	34	285	1.7	7 min.
48	184	0.4	27 min.	2 min.	35	265	2	1 min.
49	217	0.3	38 min.	4 hrs.	36	230	2	18 min.
50	212	0.3	32 min.	1 hr 18 min	40	205	2	3 hrs 5 min
51	218	0.4*	17 min.	2 min.	41	202	2	20 min.
52	174	0.4*	17 min.	1 min.	44	161	2	6 min.
53	219	0.2*	27 min.	17 min.	45	151	2	2 hrs 26 min
					46	141	2	46 min.

system. This involves inhibition of other centers and other reactions (including pathogenic ones).

Finally, it appears that the phenomena of resistance are diverse and cannot be linked to a single mechanism. However, the results of our experiments indicate that the development of nonspecific resistance may be accomplished on the basis of the principle of dominance. This is of special importance for the prevention of certain pathological processes in man, to which we shall devote the final chapter of this book.

CHAPTER V

THE PRINCIPLE OF DOMINANCE AND THE PREVENTION OF PATHOLOGICAL PROCESSES.

Criticism of Selye's Concept

The attempt made by Hans Selye to attribute all phenomena of "non-specific resistance" to processes appearing in the pituitary-adrenal cortex system, ignoring the role of the nervous system in the regulation of resistance phenomena, has aroused serious critical comments from a number of investigators. /145

In 1952 P. D. Gorizontov noted that the appearance of Selye's teachings was in itself an interesting fact, indicating that the cellular pathology of Virchoff is undergoing a serious crisis, but the ideas of Selye, aimed at replacing cellular pathology, are rather close to Virchoff's ideas. "Selye," writes the author, "has used the anxiety reaction as the result of a direct stimulating effect on the tissue of different stimulators and the setting in motion of humoral metabolic mechanisms." P. D. Gorizontov shows the lack of success of Selye's attempts to attribute phenomena of resistance exclusively to changes in the endocrine gland system, and to treat the mechanisms for development of disease merely as the consequence of inadequacy of the adaptational function of the pituitary.

"In Selye's concept, especially in his early works, he does not have an absolutely correct view of the role of the endocrine glands in the processes of adaptation, the formal breakdown of reactions, as if they existed autonomously within the limits of individual systems of the organism (especially the endocrine system)", emphasized P. D. Gorizontov later (1960), while in 1963 he wrote that it is impossible to accept Selye's concept regarding stress as a whole "because only one theme is established and developed in it (essentially the humoral one), out of the long chain of processes which occur

in the organism under the influence of extreme stimuli". On the basis of the study of one of these aspects, it is not possible to have a correct idea of the essence of the interaction of the organism and the environment under pathological conditions.... it does not follow that the processes of protection and adaptation under unfavorable life situations are accomplished only by means of development of such states of the organism which can be produced by stress or strain, taking place with mobilization of energy resources and with increased activity of the hormonal system. The reactions which have been developed by evolution in the organism may be more economical and aimed at the prevention of serious losses. Reactions of this kind are produced primarily by a change in the activity of the nervous system. /146

In analyzing Seley's concept, V. S. Smolenskiy (1955) wrote: "Selye attributes the reactions of the organism to the influence of agents in the environment to the humoral-hormonal changes. The author constructs the entire structure of his syndrome changes in the pituitary and adrenals ... it is not necessary to be a doctor to understand the narrowness and extreme one-sidedness of such concepts."

"Non-specific adjustment (adaptation) reactions, characteristic of diseases in general, are viewed by several authors from a very restricted standpoint," emphasize I.R. Petrov and Ya L. Rappoport (1958). "Thus, in Selye's opinion, the entire adaptional syndrome which arises in different diseases is caused only by an increased function of the anterior portion of the pituitary and the adrenal cortex. Without denying the protective role of the endocrine glands in disease, it is necessary to keep in mind that their activity is regulated by the nervous system, which reacts more than any other to harmful influences".

"As we know, Selye feels that all non-specific adaptational reactions, which he refers to as a general adaptation syndrome, arise as a result of the increased function of the pituitary and the adrenal cortex under the influence of strong stimuli. This explanation for the mechanism of action of extreme stimuli is very one-sided", writes I.R. Petrov (1962).

Criticizing Selye for failure to give full consideration to the role of the nervous system in reactivity, N. N. Sirotinin (1958) says: "Selye writes that the stress reactions are observed in animals which do not have a nervous system and even in a tissue culture, but Selye's assertion is without foundation, since he has not performed a comparative pathological analysis in this regard. It seems perfectly clear to us that the changes which arise in the simplest animals in response to the action of stressors and in tissue cultures differ markedly from those in higher animals ... The facts observed by Selye and his numerous followers help to clarify several aspects of the reactivity of the organism, but this school cannot pretend to explain the entire essence of reactivity."

In explaining the mechanisms of reactivity and resistance of the organism, the author stresses the important role of the nervous system in regulating the activity of many protective mechanisms and those which insure the development of compensatory reactions (Sirotinin, 1966). /147

A critical analysis of Selye's concept was given in the book by K. M. Bykov and I. T. Kurtsyn, "Cortico-Visceral Pathology" (1960). The authors write that the artificial separation of an individual discipline (endocrinology) from general physiology was the reason why the humoral theory of pathology arose among a number of endocrinologists, who developed the modern theory of panhumoralism. "Viewing the endocrine system essentially as an autonomous system of regulation, Selye feels that the very complicated set of reactions which develop in response to the action of any stimulus (including a pathogenic one) and are aimed at adaptation and adjustment is accomplished by two endocrine glands (the anterior lobe of the pituitary and the adrenal cortex)."

Teachings on stress view the pathological process as a complex of reactions that arise in the organism under the influence of a pathogenic stimulus, including not only pathological but also protective-compensatory processes. This is completely in accord with modern concepts of disease. Selye, however, attributes the critical importance exclusively to the

pituitary-adrenal system, which is activated by a humoral mechanism under the influence of extreme stimuli. The authors emphasize in this regard that they are completely in accord with the critical remarks made against this concept by V. S. Smolenskiy (1955), P. D. Gorizontov (1952, 1960, 1963), I. R. Petrov and Ya L. Rappoport (1958).

In 1965, S. M. Pavlenko wrote: "Without attributing primary importance to the nervous system in the general economy of the organism and the dynamics of development of all of its life processes, Selye nevertheless tears the organism out of its surroundings and divides it into small individual parts bearing little relation to one another. Without taking into account the reflex principle of regulation of the vital activity of all higher animals and man, he finds himself on an anti-evolutionary path regarding concepts of fundamental features of pathology".

"....The theory of 'stress' of Hans Selye, excluding the participation of the nervous system in the active reactions of the organism to a "stressor" is inadequate for explaining the mechanism of development of general pathological states," emphasizes P. K. Anokhin (1962).

In 1962, one of the authors of this book came out with a critical analysis of Selye's concept regarding chiasmic resistance, emphasizing the value or the importance of the nervous system in the development of phenomena of resistance to the action of pathogenic stimuli, noting that the facts he had obtained did not fit within the framework of Selye's concept. "The humoral changes observed by Selye cannot explain all the phenomena of resistance. At the present time, it makes no sense to compare humoral factors to nervous ones. These are two branches of a single regulatory mechanism, in which (as we know) the nervous system plays the leading role. /148
It would be senseless to repeat that the latter accomplishes its effects through the release of specific humoral agents, and that its functional state depends on chemical conditions of the medium" (Kositskiy, 1962).

A critical discussion of Selye's concept and the non-specific resistance is found in the works of N. V. Lazarev (1961) and F. G. Agarkov (1962). The

latter feels that in a state of non-specific increased resistance, the nervous mechanisms play a role which is no less important than that of the pituitary-adrenal cortex system. This system is not isolated and constitutes only one link of a complex chain that goes to make up a single neurohomoral system of regulation.

The importance of the nervous system in the increase of resistance in muscular training was shown in the studies of Z. I. Barbashova (1961), N. V. Zimkin (1962), A. V. Korobkov (1962) and other authors. B. Koyranskiy (1962), on the basis of a study of an "adaptational syndrome" caused by the prolonged action of high temperature concluded that this syndrome does not arise in the manner described by Selye; it is much more complex and diverse. Evaluation of the "adaptational syndrome" requires consideration of developing phenomena of parabiosis and protective inhibition of the central nervous system, arising as a result of a strong flow of impulses from the extero- and interoreceptors which occurs under the influence of "stressors". I. D. Gervaziyeva and P. I. Lyubovskaya (1962) concluded that the "stress" reaction, like all adaptational-adjustment reactions of the organism, is regulated by the cerebral cortex. S. M. Dionesov (1962) presents a good deal of his own and other data regarding the change in the reactivity of the organism relative to the action of a number of toxic substances and pharmacological agents (strychnine, camphor, corazol, chloral hydrate, barbiturates, histamine, heterogeneous blood, ephedrine, cocaine, phenamine) under the influence of supplementary non-specific (painful) stimuli. The author emphasizes that it would be incorrect to treat these facts solely from the standpoint of Selye's concept: "The mechanism of the protective reactions, which includes painful reflexes, is obviously more complex".

S. M. Leytes (Leytes and Lapteva, 1967), agreeing with P. D. Gorizontov (1952, 1960, 1963) writes that the "initial participant in any reaction which arises in unfavorable vital situations is almost always the sympathetic nervous system", whose adaptational-trophic significance was established earlier by L. A. Orbeli.

In studying the mechanisms of the increase in resistance during the action of supplementary non-specific stimuli, Soviet authors operate on the basis of the achievements of modern neurophysiology and on data which show the significance of the entire complex of neurohumoral mechanisms of regulation of physiological processes. /149 From an understanding of the mechanisms of such reactions, it is important to recognize the important role played by the studies of L. A. Orbeli on the adaptational-trophic effects of the sympathetic nervous system (L. A. Orbeli, 1938) as well as the work of A. D. Speranskiy (1935). In his day (1946), Speranskiy placed special emphasis on the role of the nervous reflex mechanisms in the development of non-specific resistance of the organism. He and his co-workers suggested the reception of non-specific stimuli by receptors, which successfully recommends itself to the cure of certain ailments (reflexes from the lung in tuberculosis therapy and certain other ailments, 1957; Ostryy, 1962). A. G. Ivanov-Smolenskiy (1965 emphasizes that in speaking of stress (strain) and thereby using Pavlovian terminology, Selye is really not studying the importance of the central nervous system in these reactions. He suggests that "stress" means only strain or over-strain of processes of endocrine-metabolic adaptation.

Having presented these critical remarks made by many Soviet physiologists and pathologists in regard to Selye's concept, let us now consider the facts which were not taken into account in Selye's treatment or which contradict the concept as a whole.

Let us begin with the role of the mineralocorticoids and glucocorticoids as hormones which insure development of adaptive reactions. We know that aldosterone, one of the principal mineralocorticoids, regulates sodium ion exchange in the organism, so that it has a wide spectrum of activity, being involved especially in the regulation of water exchange, diuresis, nutrition of the organism, etc. Selye is incorrect in stating that liberation of aldosterone is dependent on the action of the adrenal cortical hormone from the pituitary. In reality, however, the release of aldosterone depends on the blood volume, especially on the amount of blood entering the right heart. A change in the volume of the right auricle causes the development of signals

in the volumoreceptors of the myocardium, which acts on the hypothalamus. We know that compression of the inferior vena cava and other effects which limit the access of blood to the right heart produce a sharp increase in the production of aldosterone. On the other hand, increased dilation of the walls of the right auricle inhibits the formation of aldosterone. Both of these effects have no relationship to this so-called "stress", but belong to the area of regulation of a constant blood volume and tissue fluid in the organism. The secretion of aldosterone causes an increase in the reabsorption of sodium in the distal canaliculi of the nephrons, leading to an increase in the osmotic pressure of the blood and tissue fluid, making it possible to retain fluid in the organism, thereby increasing the blood volume. Inhibition of aldosterone secretion produces increased sodium excretion and a consequent rise in water exretion.

The production of aldosterone is stimulated by the product of the neuro- /150
secretion of the hypothalamus, with this process being accelerated with a decrease in afferent impulsation arriving at the central nervous system from the stress receptors in the right auricle. In addition, aldosterone secretion is stimulated by hypertensin (angitonin) formed in the blood plasma under the influence of renin, produced by the juxtaglomerular apparatus of the kidney. As a rule, renin is produced by the kidney when there is an insufficient blood supply. Consequently, the autoregulatory mechanism operates in this case as well: angiotensin, stimulating the production of aldosterone, causes an increase in the volume of circulating blood and this leads to an improvement of the blood supply to the kidneys.

The level of aldosterone plays an important part in the regulation of nutrition and the degree of thirst (Arkind, 1968). Hence, generally speaking, the mineralocorticoids are not adaptive hormones. They play a different role; their influence on inflammation reactions is only a side effect, and the regulation of their excretion has no relationship to reactions which Selye designates as "stress".

As far as the role of the so-called "anti-inflammatory" hormones is

concerned, i.e. the glucocorticoids, it is hardly possible to suggest that the inhibition of the inflammation process is an expression "of adaptive reactions" which always insure adjustment and protection of the organism under the influence of extreme stimuli.

As we know, in the course of evolution the inflammation reaction developed as a protection reaction, so that inhibition of this reaction cannot be viewed as an expression of a state of "adaptation" and "resistance". In fact, it was shown even in Selye's experiments that the inflammation reaction which develops following the injection of croton oil produces a granular torus, protecting the surrounding tissue from death. A decrease in the inflammation reaction with simultaneous injection with glucocorticoids is accompanied by the development of tissue necrosis (Selye, 1954).

We know that the glucocorticoids, inhibiting inflammatory reactions, retard the healing of wounds. For this same reason, by inhibiting the development of the protective granular torus when microorganisms are injected into the skin, the glucocorticoids permit a generalization of the infection process. The glucorticoids also inhibit the specific immunological reactions of protection, which reduce the resistance of the organism to infectious diseases. By retarding the synthesis of interferone, the glucocorticoids have an unfavorable influence on virus infections (Gorizontov, Protasova, 1968).

It is hardly likely that such an effect of the glucocorticoids would be an effect that promoted "adaptive" reactions, i.e., a reinforcement of resistance and protection of the organism, as Selye states. /151

It should also be emphasized that stimulation of excretion of ACTH by the anterior lobe of the pituitary (regulating the secretion of glucocorticoids) is not accomplished by the action of a "metabolite" which develops in the tissues under the influence of stressors, as H. Selye proposed.

The activity of the pituitary is regulated by the hypothalamus, while

the production of hormones from the anterior lobe of the pituitary, including ACTH, depends on the action of substances produced by nerve cells of the hypothalamus on the pituitary.

An important role in the mechanism of regulation of the functions of the anterior lobe of the pituitary is played by the features of its blood supply, and especially the fact that they are common for the hypothalamus and for the anterior lobe of the pituitary. The blood, flowing from the capillaries of the hypothalamic region reaches the so-called portal vessels of the pituitary and washes the cells of the pituitary. The hypothalamic region around these capillaries contains a nerve network composed of nerve cell processes, forming its own neuro-capillary synapses in the capillaries. Through these formations, the products of neurosecretion (i.e., the physiologically active substances formed by the nerve cells of the hypothalamus) enter the blood and travel directly to the cells of the anterior lobe of the pituitary with the blood flow, stimulating its function. Hence, the secretion of the anterior lobe of the pituitary is regulated by the central nervous system, i.e., by special nuclei in the hypothalamus, so that the regulatory effects are accomplished by humoral means. The substance which stimulates the production of ACTH and has been called the corticotropin-realizing factor (CRF) is a polypeptide, the product of the neurosecretion of the neurons of the hypothalamus. "...Neurons with the secretory function form the morphological and functional bridge which permits the transformation of brief impulses into relatively stable, powerful humoral effects on the organism" (Voytkevich, 1967).

Surveys of papers dealing with the problems of neurosecretion have appeared in monographs by Ya Sentagotai, B. Flerko, B. Mesh, B. Khalas (1965), K. Lishshak and E. Edretsi (1967) et al.

The discovery of the phenomena of neurosecretion has opened up an important branch which combines the processes of nervous and humoral regulation into a single system of processes for neurohumoral regulation of the functions of the organism. It had been found that the nerve cells participate in the regulation of functions not only by generation of nerve impulses and secretion

of mediators, but also by production and excretion of many specific high-molecular substances of a polypeptide nature, which possess the typical properties of hormones.

However, in contrast to the glandular cells, the neurons which produce hormones also possess the ability to generate and transmit nerve impulses, i.e., they possess specific properties that belong to nerve cells. In addition, secretion of hormones by nerve cells occurs when these cells are stimulated, in a process which is characterized by pulse potentials.

Hence, the brief action of the nervous system on the organs and tissues, /152 accomplished through a nerve impulse, is reinforced by the long-term effect of biologically active substances of a hormonal nature.

It is important to note the multistage nature (sequence) of this influence of the neurohormones. The neurohormones of the hypothalamus stimulate the pituitary, intensifying the production in the latter of corresponding "trophic" hormones (in our case ACTH), but the latter, acting on the adrenal glands, lead to the production of hormones which have a direct influence on the function of organs and tissues in the organism. This "multi-cascade nature" of the humoral links of the neurons of the hypothalamus to the cells of the organs and tissues allows a certain economy in regard to the regulatory processes, i.e., changes in large cell territories of the organism can be achieved by the secretion of comparatively small amounts of neurosecretions. Each "stage" of such a link is an independent "amplifying stage" (similar to what occurs in electronic amplifiers). On the other hand, such a system of "multi-stage circuits" allows finer regulation of the level of excretional hormones, doubling the mechanisms for feedback in each "stage" of this multi-branched system.

When extreme stimuli are acting on an organism, an increase in the secretion of glycocorticoids takes place as the result of stimulation of production of the cortictropin-stimulating factor of the hypothalamus, produced by afferent nerve impulses, signaling the influence of an extreme

stimulus. In addition, ACTH is excreted under the influence of adrenalin and noradrenalin, created by the adrenal cortex. It has been determined recently that adrenalin stimulates the excretion of ACTH, acting directly on the anterior lobe of the pituitary, and that this effect is retained even after transplantation of the pituitary to other parts of the body and the absence of its connections to the hypothalamus.

Hence, Selye's concepts regarding the humoral mechanism of excretion of adaptive hormones under "stress" are incorrect. The excretion of glycocorticoids is accomplished by the participation of the nervous system in the reaction to extreme stimuli and the subsequent stimulation of the function of the adrenal cortex by two pathways: by means of the excretion of adrenalin and by the excretion of the corticotropin-stimulating factor of the hypothalamus.

In both cases, the process for production of ACTH, and therefore the maintenance of the necessary level of this substance in the blood, as well as the process of excretion and maintenance of glucocorticoids at the required level in the blood, is set in motion and continues to be controlled by regulatory impulses originating in the nervous system.

Consequently, the theory regarding the humoral "autoregulation" of the excretion of "adaptive" hormones in the form of some kind of autonomous phenemonon, selected from the complex processes of neurohumoral interaction, is the result of a unilateral (or even insufficiently competent) approach to the study of the mechanisms for regulation of physiological functions, including processes of adaptation. /153

Although it is assumed a priori that humoral regulation was the more ancient form of regulation of functions, and the nervous system is a faster way of transmitting signals and arose later during the process of evolution, the situation is actually the reverse. The capacity for more rapid induction of stimuli along certain structures appeared simultaneously with the development of the ability to move, i.e., in the very earliest stages of development

of animal organisms. Even in unicellular animals, which have specialized organs for motion in the form of flagella or cilia, there is a special fibrillar system (neurofans), which have the ability to rapidly transmit excitation to these organs of movement. The simplest multicellular animals, the Coelenterata, which have nonskeletal motorics, do have a specialized nerve system located in the motor apparatus itself. In conjunction with the diffuse nature of the motor apparatus, there is also a diffuse nature of the structure of the nervous system at this stage of development.

With a transition to a more complex form of motion, to peristaltic motion, in which there is successive participation of individual segments of the body in motor activity, a new type of structure is developed for the nervous system — a ganglionar nervous system. The appearance of more complete forms of movement, linked with the development of a skeleton, leads to the development of a central nervous system — as well as a spinal cord and brain (Sepp, 1959).

Hence, the development of the nervous system is an intrinsic feature of the evolutionary development of the animal world in general.

The humoral interrelationship between cells is the simplest and most widespread form of interaction. It is necessary to emphasize, however, that the adrenal glands themselves, as specialized organs, appeared and developed in the course of evolution much later than did the nervous system, and from the very beginning of their development have been and remain "helpers" for the nervous system in accomplishing its regulatory effects on the organs and tissues.

The development of such a "helper" made it possible to have a more "economical" control of the vegetative functions of the organism. In those cases when it is necessary to create a prolonged "background" of regulatory effects, and when it is necessary to accomplish regulatory effects continuously over a long period of time, it is better to have effects that are realized by the excretion of special biologically active substances, produced /154

by the adrenal glands. Even certain tonic effects of the nervous system itself, development and growth of certain dominances (Ukhtomskiy, 1923, 1925), processes of prolonged adjustment of the level of functioning and the very structure of the organs and tissues, are accomplished in the organism by means of the excretion of hormones whose production is regulated by the nervous system. In this regard, nerve impulses are relatively insignificant in terms of their energetic power (but they do carry important information for homeostasis), and they are able to produce prolonged changes in function (and structure) in large cell territories of the organism.

Hence, assembling the picture of the processes of regulation of any functions of an organism (including regulation of the phenomena of adaptation and resistance (selecting a particular aspect or aspects) from a complex assortment of regulatory reactions and disregarding the other elements is completely senseless. This would be equivalent to an attempt at composing a poem using only one or two letters of the alphabet.

Anyone who puts together any kind of a general biological theory must also take into account the role, significance and interaction of all aspects and elements of regulation.

However, making these additions to Selye's theory on "stress", and emphasizing the participation of the nervous system in the regulation of excretion and maintenance of a certain level of "adaptive" hormones in the blood, makes it possible to limit these modernizations of Selye's concepts and to think that the processes of resistance are achieved by the action of certain "adaptive" hormones, while the nervous system is assigned merely the role of a mechanism which regulates the excretion of these hormones.

It seems to us that such a treatment would be an extreme simplification of the real picture of the diverse protective and adaptive reactions of the organism which are regulated by the nervous system.

The development of nonspecific protective and pathological reactions is not included in the system proposed by Selye. The concept of "stress" cannot be used as a basis for explaining many phenomena, especially the information we obtained regarding the inhibition of pathological processes under the influence of supplementary nonspecific stimuli, described in the preceding chapters.

According to Selye, the action of cold is a powerful "stressor", and the freezing and death which occur indicated that the adaptive possibilities of the organism were exhausted (depleted). It then becomes impossible to understand why the application of another "stressor" (an electric current) against this background, which would be expected to cause still faster depletion, actually prevents the death of tissues. Death comes when adaptation is "exhausted". An increase in stimulation, according to Selye, should /155 speed up exhaustion. Instead, the supplementary stimulus protects the animals against death. Selye's concept does not cover the results of experiments in which the pathogenic stimulus precedes the nonspecific one. In this order, their action, not only does not inhibit the pathological process, but intensifies it. Similar phenomena were described a long time ago by A. D. Speranskiy (1935) under the name of "second shock". In the case of allergic reactions, they are known by the name of "parallergies".

In the studies which we conducted of the interaction of reactions to tuberculin and the subcutaneous injection of turpentine in sensitized guinea pigs, we found that, although the turpentine acted jointly with the tuberculin on the animals for several days, the critical factor, as far as the outcome of the process was concerned, was the difference in the time of their application, which was reckoned in minutes.

The system proposed by Selye fails to take into account many other reactions of the organism which develop under the influence of pathogenic agents. "Undoubtedly, the excessive reaction of glucocorticoids is of considerable importance in the formation of adaptational reactions, but it would be incorrect to attribute the main and basic role to this process," writes

S. M. Leytes. Following removal of the adrenals, animals can develop a general adaptational syndrome if they receive a daily injection of a minimal and constant amount of corticosteroids (experiments of Ingle, 1956), while, according to Selye, a general adaptational syndrome would necessarily involve an increase in the secretion of hormones. In these experiments (Ingle, 1956) the corticosteroids played a permissive role, i.e., their presence was necessary for the appearance of other factors participating in the realization of adaptational phenomena" (Leytes and Lapteva, 1967). These problems were studied in detail in the monograph by P. D. Gorizontova and T. N. Protasova, "The role of ACTH and corticosteroids in pathology" (1968). "Recognition of humoral reactions as the cause of illness in an organism leads to failure to consider the role of etiological factors and overestimation of the role of the internal properties of the organism, i.e., to conditionalism in modern pathology," the authors write. Thus, on the basis of the similarity of pathological processes which developed as a result of an overdose of hormones in arthritics, Selye views arthritis in man as a disease caused by an excess production of inflammatory hormones. This is the erroneous result of a one-sided view. Clinical studies show that rheumatoid arthritis is found in patients with Addison's disease and in hypopituitarism. The observed facts are in direct contradiction to Selye's concepts (page 104).

"Many reactions which Selye viewed as the result of the influence of an excess production of hormones in reality are independent of the action of the hormones themselves. The role of hormones is secondary in many reactions." (same source, page 104). /156

"Selye's system, dividing diseases into those which arise as the result of the dominance of the influence of either inflammatory mineralocorticoids or anti-inflammatory glucocorticoids, has been found to be invalid. In reality, there is no such dualism in the development of the pathology which serves as the focus in Selye's schemes" (same author, pages 104-105).

Hence, even when we add the missing link to Selye's concept, i.e., after showing the role of the nervous system in the regulation of excretion of

"adaptive hormones", we still cannot accommodate the enormous number of observations made in modern pathology in the Procrustean bed of Selye's concept and attribute the problem of participation of the nervous system in adaptive reactions of an organism to the regulation of excretion of corresponding hormones alone. In this connection, it is necessary to dwell in greater detail on the problem of the role of the nervous system in the development of protective reactions of the organism and the increase in resistance to the action of extreme stimuli.

The Role of the Nervous System in the Increase of Resistance of an Organism Under the Influence of "Stressors"

Without de-emphasizing the significance of the facts obtained by Selye in regard to the participation of "adaptive hormones" in the reactions that occur during the influence of "stressors", we must emphasize again and again that the reasons for the increase in resistance cannot be attributed merely to an increased production of adaptive hormones and are in reality much more complicated. This fact must be emphasized in view of the fact that certain authors, attempting to "supplement" Selye's teachings with data on the role of the nervous system (and especially the hypothalamus) in the regulation of the function of the pituitary and the adrenal cortex, suggest that this method will serve to "reconcile" Selye's concepts with modern nervism.

However, "the importance of the nervous system is determined, not only by its role as an initiating mechanism, but also by its ability to change both quantitatively and qualitatively the reactions which occur in various organs," P. D. Gorizontov (1963) correctly pointed out.

As we know, the effect of different pathogenic agents on the organism, including, according to I. P. Pavlov (1900), "extreme stimuli", i.e., usual "physiological" stimuli, which are sharply intensified as far as the strength or duration of action are concerned, produce (along with phenomena of disruption, damage, "breakdown of mechanisms") protective reactions of the organism at the same time. In the words of I. P. Pavlov (1935), the doctor

must be able to differentiate between the protective reactions, so that at certain periods in a disease he will be able to reinforce them and thereby /157 contribute to a cure. I. P. Pavlov (1930) called such reactions "a physiological measure against disease", giving as an example the development of mucous membrane inflammation (catarrh) of the stomach when its walls are burned, the development of protective inhibition of higher sections of the central nervous system in the event of overstimulation, which prevents the exhaustion of the cells of the cerebral cortex, etc. This state, on the one hand, is a disease as I. P. Pavlov (1930) emphasized, since it denies the patient the possibility of a normal interaction with the environment, but, on the other hand, by virtue of the very mechanism of its development, it is a protective reaction of the organism, "a physiological measure against disease", which promotes more rapid recovery.

The majority of the so-called "typical pathological processes" which we discussed in the first chapter, along with the phenomena of damage, also contain elements of protection, reinforcement, "physiological measures" (or are even the result of the excessively developed protective reactions mentioned).

It is conventional to divide protective reactions into specific and nonspecific ones. The former include immunological reactions, adaptation to the effect of changes in barometric pressure, temperature (tempering), humidity, gas composition of the surrounding medium, and many others. The intensity of the activity of protective mechanisms, which allow these reactions to take place, is regulated, as a rule, by the nervous system. An increase in the activity of the nervous system, or a rise in its tonus, leads to an improvement in the function of these protective mechanisms.

Therefore, the action of supplementary nonspecific stimuli which produce an increase in the tonus of the nervous system may be accompanied by an increase in the function of specific protective mechanisms and may also mean an increase in the resistance of the organism to the effect of unfavorable factors.

However, the nervous system regulates the intensity of the occurrence, not only of specific, but of nonspecific protective reactions. These include reactions of barrier mechanisms, inflammatory reactions, reactions of "nonspecific immunity", phagocytosis, increased body temperature (fever), activity of the excretory organs, etc., as well as protective inhibition of the higher sections of the central nervous system (according to I. P. Pavlov). The operation of all these mechanisms, producing nonspecific protective reactions, is also regulated by the nervous system. In this connection, it is understandable that these reactions also depend on the nature of higher nervous activity (Kavetskiy, Solodyuk, Vovk, Krasnovskaya, Dzgoyeva, 1961, et al).

The dependence of reactions which reinforce the nonspecific resistance /158
of the organism upon the regulatory effects of the nervous system is demonstrated by numerous pharmacological studies which have shown that many neurotropic substances are capable primarily of stimulating phenomena of nonspecific protection. These problems have been studied in detail in the work of N. V. Lazarev ("Handbook of Pharmacology", 1961).

This makes it possible to understand the fact that supplementary nonspecific stimuli which cause excitation of the central nervous system may also cause a sharp increase in the nonspecific resistance of the organism. It has been part of medical practice for a long time to make widespread use of cures involving the action of various nonspecific stimuli on the organism. Such stimuli include local "distracting" devices, many physiotherapeutic procedures (Obrosov, 1962), massage (Verbov, 1966), the use of cups, plasters, parenteral injection of foreign proteins, local heating or cooling of tissues, acupuncture, etc.

A special place is occupied among the protective reactions by the compensatory processes in which an important role is played by the conditioned reflex activity of the cerebral cortex (Asratyan, 1936, 1948, 1953).

Along with the features and differences for all of these effects, there are also certain characteristic general features, which include the ability

to stimulate the protective reactions of an organism, as well as the reactions which insure the phenomena of nonspecific resistance. We know that some of these effects lead to an increase of production of the "adaptive" hormones, but it is possible that the mechanism of a favorable action on the organism of these devices and methods of curing does not act on this alone.

The stimulation of protective reactions of the organism often occurs under emotional stress. The studies of P. D. Simonov (1966, 1968) indicate that negative emotions arise with a lack of "pragmatic information", i.e., information on how to approach a difficult situation, requiring mobilization of all the forces of the organism. The vegetative changes which occur in emotional excitation are aimed at the mobilization of the organism's resources for escape from a difficult situation (Cannon, 1922).

Although it is known at the present time that emotional stress provokes the development of certain diseases in many cases, especially diseases of the cardiovascular system (so that individuals are often advised to avoid emotional reactions in situations which could produce negative emotions), it is necessary to note that the emotions themselves arose as in the process of evolution as valuable auxiliary reactions (Kositskiy, 1965a, 1966a). They not only mobilize the resources of the organism for increased physical and intellectual activity, but in many cases reinforce the functions of the protective devices of the body.

Hadnagy and Kovats (1954) showed that emotional stress in students during /159
examinations increases the phagocytic activity of the leucocytes. Similar changes in the phagocytes occurred in the presence of defensive conditioned reflexes (Muksinova, 1955). Increased phagocytosis has also been observed when adrenalin was injected. However, emotional states accompanied by an inhibition reaction (horror), experimental neurosis, the action of a drug, etc., lead to inhibition of phagocytic activity of the leucocytes. Increased phagocytic activity arises during painful stimuli. However, severe pain inhibits phagocytosis.

A detailed survey of literature on the changes in the phagocytic activity in the presence of painful stimuli are found in monographs by A. D. Ado (1961a) and F. M. Dionesov (1963).

The method of using supplementary nonspecific stimuli to increase protective reactions was used by A. D. Speranskiy, et al, to cure tuberculosis and other ailments (1957).

We are presenting these facts here to show that supplementary nonspecific stimuli increased the resistance of the organism, not only by the excretion of adaptive hormones (causing phenomena of so-called "chiasmic resistance", according to H. Selye), but also by the stimulation of a large complex of auxiliary reactions of the organism in the excitation or increasing of tonus of the central nervous system.

It is necessary to emphasize, however, that the results of our similar investigations described in the preceding chapters of this book indicate that the reason for inhibition of pathological processes may also be the development of dominance in the nervous centers. As we mentioned earlier, our observations indicated that the critical factor which prevents the development of pathological processes is the sequence of action of a pathogenic and a supplementary (nonspecific) stimulus.

If the supplementary (nonspecific) stimulus is given before the pathogenic one so that the latter acts against the background of the influence on the organism produced by a supplementary (nonspecific) stimulus, the development of the pathogenic process is inhibited. However, if the stimuli are interchanged in time and the pathogenic stimulus is given first, followed by the supplementary (nonspecific) one, the pathological process, not only will not be inhibited, but, on the other hand, will be reinforced and will lead to rapid death of the animal in many cases.

The sequence of action of the stimuli was also found to be the critical factor for preventing physiological processes which develop over a period of

days (for example, tuberculin allergy). Then the difference in time of application of the supplementary and specific stimuli, equal to several minutes, turns out to be critical for the development or inhibition of the pathological process.

These facts are not included either in the system of phenomena of "chiasmic resistance" proposed by H. Selye, or in the concepts given above regarding the intensification of nonspecific protective reactions of an organism in response to any excitation of the central nervous system. /160

To explain these facts, we must obviously use the fact that stimuli which act on the nervous system and have sufficient intensity, as we know, produce the appearance in the central nervous system of a "focus" of dominant excitation, which changes the nature of the reactions of the organism to other stimuli, so that the stimuli produced by them lose the ability to evoke specific reactions for given stimuli and begin to reinforce the existing "dominant focus".

The view that the basis of these facts is the phenomenon of dominance is reinforced by the fact that inhibition of pathological processes is noted only at a certain (moderate) intensity of supplementary nonspecific stimuli, when they have produced characteristic changes in the general behavior of an animal, usually inhibition.

One might think that under these conditions the central nervous system would see the development of a focus of excitation which inhibited the other reactions by virtue of the principle of "negative induction" or "external inhibition" (according to I. P. Pavlov). On the other hand, the action of stimuli that are too mild or overly strong, since they do not cause general inhibition of the animal's activity, are not accompanied by inhibition of pathological processes either.

As we know, in accordance with the data obtained by I. P. Pavlov and his associates, the slight stimulation of the central nervous system which

occurs under the influence of mild stimuli causes irradiation of the excitation process over the entire central nervous system and makes possible an increase in its general tonus. In our experiments, weak stimuli did not prevent the appearance of pathological processes. With increased stimulation, there is a strong "focus" of excitation which develops, and the nature of the influence of this "focus" on the other parts of the central nervous system changes radically. A strong "focus" of excitation induces opposite processes in other parts of the central nervous system. This causes a state of "external inhibition". It is precisely these powerful stimuli which in our experiments prevented the development of pathological processes.

However, if the intensity of the stimulus is increased still further, the result of generalization of the excitation process, i.e., its spread to other parts of the central nervous system, will result in the development of a state of severe general motor excitation of the animal, as well as stimulation of vegetative centers.

In our experiments, very strong stimuli, which produced similar states /161
in the central nervous system, failed to prevent development of pathological processes.

These facts also speak in favor of the view that the cause of inhibition of pathological processes in our experiments was apparently the development of a dominant "focus" of excitation under the influence of the action of a nonspecific stimulus.

This viewpoint is also supported by the fact that under the influence of supplementary nonspecific stimuli, not only pathological processes were inhibited, but also other reactions of the organism to the action of nonpathogenic ("test") stimuli.

Thus, we tend to view the inhibition of pathological processes observed in our experiments against the background of the action of supplementary

nonspecific stimuli as the result of a process of inhibition of those areas of the central nervous system which participate in the realization of the action of a pathogenic stimulus.

In this case, the inhibition of the pathological processes is analogous to that which takes place with general inhibition of the central nervous system of an animal (for example, under the influence of drugs, hibernation, etc.). But how can we match such concepts with the facts presented above in this chapter?

To be sure, the nervous system regulates the processes of protection for the organism against pathogenic influences. Why does the inhibition of the nervous system, accompanied by inhibition of certain protective reactions, not reinforce the pathological processes instead of preventing their development?

It seems to us that the reason for this depends on the condition that there is nothing which is absolute in nature, and there is no such thing as absolutely favorable "protective" reactions in the organism.

In those stages of development of a disease when the protective reactions are very much in evidence, they can (as we said earlier) reverse their effect and begin to constitute a threat to the organism. Obviously, it is desirable in such cases to inhibit such "protective" reactions.

Our principal experiments were performed on the model of adrenalin pulmonary edema. This is a protective reaction as far as the mechanism of its origin is concerned. It is the result of increased excretion of water from the alveoli of the lungs with increased blood pressure in the lesser circulation. This "stress reflex" in response to toxic doses of adrenalin assumes such magnitude that it itself causes the death of the organism, due to filling of the alveoli with transudate, preventing gas exchange (Kam, 1953). In this case, suppression of this "protective" reaction means the death of the organism.

Obviously, it is impossible to simply take all the phenomena involved /162
in life, put them into boxes, and stick labels on them inscribed "Helpful" and "Harmful". Any phenomenon can be helpful or harmful only under given concrete conditions. Of course, certain favorable reactions, when intensified, can have the opposite effect.

Excessive development of certain protective reactions can itself lead to death of the organism. Thus, for example, an increase in temperature in an infectious process, as we know, is a protective reaction, but an increase of temperature above 42° will lead to death. Inflammation is a protective reaction on the part of the organism. But a sharply pronounced reaction of inflammation (especially in organs important for life) can itself lead to death. The growth of granulations is a protective barrier that protects the internal medium. But a scar develops on the site of the granulations, preventing the restoration of tissue and function. The secretion of mucus by the gastric glands is a protective reaction which prevents damage to the walls of the stomach, but in excess it itself seriously disturbs digestion, etc.

Inhibition of protective reactions in the event they themselves begin to constitute a threat to the organism may prevent pathological processes. In these cases, it may be effective to use a novocain block, narcotic substances and methods which selectively block certain branches of the reflex arc. G. S. Kan (1962), for example, showed that streptomycin, by inhibiting reflexes from chemoreceptors, increases the resistance of the organism to the action of a number of unfavorable factors. By the way, the mechanisms of this phenomenon are also not covered in the system of "chiasmic resistance" posed by Selye (Kositskiy, 1963).

Since auxiliary protective reactions, when intensified, can have the opposite effect, i.e., can themselves become pathological, then it is certainly valid to say that a disease is the appearance of adaptation of an organism (Davydovskiy, 1962). Protective supplementary reactions cannot be divided into "universal" and "uniquely possible". Life is more complicated

than this system, and reactions that begin as protective ones often become the opposite and are themselves the cause of death of the organism (Kositskiy, 1965d). This is the dialectic of life.

Inhibition of pathological processes in the development of inhibition in the central nervous system is not merely the result of a drop in the intensity of such extremely pronounced "protective" reactions.

Inhibition of the nervous system inhibits pathological processes, obviously, and therefore the actual phenomena of damage ("breakdown") which arise as the result of action of pathogenic stimuli often involve the participation of the nervous system through the agency of "pathological reflexes" (Ado, 1963). We know that in some cases it is possible to have formation of conditioned pathological reflexes which are able to cause significant disruption of functions and even destruction of the organism (Dolin, 1952, 1962). /163

The study of the corticovisceral nature of the pathogenesis of disease (Bykov, Kurtsyn, 1960) showed that the development of certain diseases sees an important role played by the phenomenon of the pathological reflex cycle ("vicious circle"), formed between the diseased organ and the subcortical centers which regulate its activity.

I. P. Pavlov repeatedly emphasized that an extreme stimulus can produce an isolated diseased point in the cortex of a diseased hemisphere, whose excitability is sharply elevated in comparison to the "excitability of other points" in the cortex. In many of these cases, the development of a pathological process takes place with the participation of the development of a "pathological dominant" in the central nervous system. In all of the cases described above, inhibition of the nervous system may be accomplished by inhibition of these pathological processes.

We know, however, that general inhibition of the central nervous system (sleep, anesthesia, etc.) as a therapeutic effect is a "two-edged sword",

since the inhibition of the pathological reflexes proper and the "pathological dominant" is accompanied by inhibition of protective reactions that are necessary to the organism at the moment. Deep curative sleep, for example, as we know, sharply weakens the intensity of reactions of immunity, phagocytic activity and many other protective reactions that cause a worsening of the course of infectious diseases, tuberculosis, etc.

An advantage of the principle of "external" inhibition is the fact that it makes it possible to suppress the formation of "pathological" dominants, without simultaneously producing a marked inhibition of the functions of the organism regulated by the nervous system which are important for life.

Hence, we can conclude that the formation in the central nervous system of a focus of dominant excitation under the influence of supplementary ("nonspecific)) stimuli is able to inhibit the development of many physiological processes with subsequent action on the organism of pathogenic stimuli, and this fact obviously has been used successfully in the clinic in many situations.

Use of the Principle of Dominance in Clinical Practice /164

Clinical medicine has accumulated many facts which indicated that the formation of a focus of dominant stimulation is able to suppress the development of many pathological processes. Some of them, in terms of the fine details in the observations, approach the results of physiological experimentation.

In 1959, Gerdner and Liklider (1964) noticed that the action of a high-intensity sound stimulus suppresses the sensitivity of a patient in stomatological operations, making it possible to conduct extensive surgical intervention without giving anesthetic. Liklider (1964) generalized the results of observations on many patients, who had been operated on with only this method of anesthesia. The method consists of the following: "The patient puts on earphones and adjusts the sound stimulus acting on him by means of

an adjustment device mounted on wheels near him. The device has two adjustments, one for music and the other for a roaring sound, produced with the aid of amplification of so-called "white" noise. At the beginning, the patient selects the music which he would like to hear (stereophonic magnetic recording), and adjusts the volume suitable for listening under ordinary conditions. When the dentist begins to work, or when his work causes a certain degree of discomfort, the patient turns up the volume of the music. As soon as he feels a slight pain, or when the doctor suggests the possibility of pain, the patient switches the adjustment device and sets the intensity of the roaring noise, which resembles the noise of a waterfall. The total sound pressure can reach up to 116 decibels. In most cases, the intense noise suppresses or eliminates the pain." (1964, page 24).

In studying the results of operations on more than 1,000 patients, it was found that total anesthesia was used in 65% of the cases, significant suppression of pain was noted in 25% and, consequently, the painless method was effective in 90% of the cases. On subsequent visits, the patients preferred the sonic pain killer to the medicinal variety. A. A. Topchibashev reported in 1966 on the favorable influence of music on patients during operations under local anesthesia.

It is possible that in all these cases the action of the supplementary sound stimulus produces a focus of dominant excitation in certain portions of the cerebral cortex, and thereby supresses reactions to other stimuli, including painful ones.

These examples are not the only ones. Supplementary stimuli associated with the purposes of therapeutic exercise, physiotherapeutic procedures, curative massage, "stimulation therapy" and other effects may have a favorable influence on the course of many pathological processes, apparently largely due to the results of the development of a new dominant.

The further development of studies in this direction appears to us to be very fruitful. This will confirm in particular our experimental observations /165

on the possibility of preventing death of an organism from myocardial infarct and other heart damage through the preliminary action of supplementary non-specific stimuli.

Use of the Principle of Dominance to Prevent Death of an Organism with Damage to the Coronary Blood Circulation in Experiments

In experiments conducted by our graduate student, G. F. Stralkov, Z. A. Nechayeva, et al, it was shown that the formation of a focus of dominant excitation may prevent the death of an organism under such severe effects as ligation of the main trunk or the descending branch of the left coronary artery in dogs.

In all 40 control experiments, this intervention led to extreme ischemia of a large mass of the myocardium, causing the development of fibrillation, and then to death of the animal 3, 5 or 10 minutes after ligation. In the next group of experiments on 10 dogs, this effect was applied against the background of a preliminary stenosis of the descending portion of the thoracic aorta. Partial blockage of the lumen of the aorta in these experiments caused a significant change in hemodynamics; the pressure in the arteries of the cephalic portion of the organism fell by 1, 1.5 or 2 times, while the pressure in the arteries of the thoracic cavity and rear extremities (below the site of stenosis) fell to 50 to 60 mm Hg.

In the cases when the trunk was ligated against this background as in the controls, or when the branches of the left coronary artery were ligated, fibrillation of the heart and death of the organism did not occur, regardless of the fact that the ligature compressed the coronary artery for 20 minutes or more and led to obvious severe macroscopic changes in an extensive ischematized region of the myocardium.

Hence, preliminary intervention in the processes of hemodynamics prevented death of the animal from myocardial ischemia.

This effect may depend on a pressure increase in the mouth of the aorta, which for purely hydrodynamic reasons may improve the conditions for collateral blood circulation in the ischematized portions of the myocardium. The possi- /166
bility is not excluded, however, that intervention in hemodynamics produced a significant flow of nervous impulses from the vascular reflexogenic zones and this impulsation may have caused the development of a focus of excitation in the central nervous system, which, according to the principle of negative induction, inhibited the reaction of the heart and the organism as a whole to the myocardial ischemia.

In the next group of experiments (on 14 dogs) two silver electrodes were implanted in the wall of the descending portion of the thoracic aorta (each consisted of a circular disk 8 mm in diameter), 20 mm apart. Electric current with a frequency of 15 to 50-100 Hz was supplied to the electrodes, with the voltage being increased gradually from several volts to 20-30 volts. This procedure did not produce any significant changes in the total arterial pressure. Then, against a background of the current's action, the same ligation as in the preceding experiments was performed on the left coronary artery. In 11 of these experiments, fibrillation of the heart muscle did not develop, and the arterial pressure remained as it was before ligation of the artery, regardless of the total ischemia of a large mass of myocardium and the pronounced macroscopic changes which occurred only 20 minutes after blockage of the lumen of the artery and destroyed the function of a significant part of the myocardium of the left ventricle.

Hence, the influence of a supplementary stimulus not accompanied by a change in the level of total arterial pressure turned out to be a way of preventing serious complications arising as a result of the interruption of the blood supply to a significant area of the myocardium (which would lead to rapid death of the organism under ordinary conditions). In this case, we prevented primarily the development of extrasystolic arrhythmia and fibrillation of the heart muscle, which indicates the dependence of these reactions on the state of the central nervous system.

The role of the central nervous system in the development of arrhythmia and fibrillation of the heart is a fact which was known to the clinicists (Sigal, 1958; Chernogorov, 1962, et al.)and the experimenters. In the laboratory of S. I. Frankshteyn, V. S. Lifshits (1954) noted that when the heart muscle is damaged, the change in heart rhythm and excitability of the myocardium has a reflex nature. B. M. Federov (1963) obtained considerable experimental data on the role of the nervous system in the development of arrhythmia. V. V. Parin and B. M. Federov (1967) note that the action of a supplementary stimulus causing certain reflex reactions in the organism (for example, the act of swallowing) are simultaneously accompanied by inhibition of ventricular extrasystole and development of a nomotopic heart rhythm.

We cannot exclude the possibility that further study of the influence of supplementary nonspecific stimuli on the processes of the development of fibrillation may be valuable in working out practical methods of preventing this serious complication of myocardial ischemia and other heart damage.

Interesting data have been obtained on the possibility of suppressing /167
serious symptoms of pituitrin coronary insufficiency, leading to the death of animals under the influence of a supplementary nonspecific stimulus. In experiments which we conducted together with a student, A. Y. U. Katkov, we found that the intravenous injection of pituitrin (1.2 ml of preparation per 100 grams of weight, activity of the preparation 5 units per ml) causes death of healthy white rats from symptoms of severe coronary insufficiency in 1-5 minutes. Preliminary injection of 0.2 to 0.4 ml of turpentine into the peritoneal cavity 10 to 15 minutes prior to injection of a toxic dose of pituitrin leads to an increase in the resistance of the animals. Out of 16 experimental animals, 10 remained alive, although the electrocardiograms showed pronounced symptoms of myocardial ischemia.

The results of these studies are felt by us to be extremely premature, but they show that this problem deserves further investigation.

All of the information presented above indicates the important role of the principle of dominance in working out ways to prevent certain pathological processes. In this regard, we must discuss the problem of mechanisms of development of the dominant itself.

Mechanisms of the Dominance

A. A. Ukhtomskiy viewed the development of a dominant as a result of a gradual, optimal increase in the excitability of a certain group ("constellation") of centers, caused by the action of afferent impulses or chemical (humoral, hormonal) agents. The theory of A. A. Ukhtomskiy meant that the action of a stimulus of a certain intensity causes the appearance of a "focus of excitation" or raises the excitability of certain points.

In recent years, important new information on the dominant has been obtained by V. S. Rusinov (1948, 1956, 1965, 1969). He proposed a model for the development of a dominant focus by means of polarization of the d. c. anode of the motor region of the cerebral cortex. The advantage of this method is not only that the state of dominance and certain parameters of the current develops very reliably, but also that the properties of the dominant focus may be evaluated and studied both in terms of the muscular reactions of the animal (motor and electrophysiological) and on the basis of the bioelectric activity of the neurons of the dominant focus itself. The latter fact makes it possible to have a very precise study of the conditions of formation of a dominant focus and the nature of the interaction of the afferent impulses reaching this focus (under the conditions of not only an acute, but also of a chronic experiment).

The studies conducted by V. I. Rusinov's associate, A. A. Sokolova /168
(1957-1969) using the method of implanted macro- and microelectrodes in a chronic experiment, showed that in the zone of the dominant focus there is a convergence of responses to stimulation of different modalities and an increase in the available activity under the influence of afferent stimuli.

An important role in this increase of activity is played by currents of afferent impulses, reaching the cerebral cortex along nonspecific afferent pathways (through the reticular formation of the brain stem).

Data on the role of the reticular formation and phenomena of concentration of attention on certain signals and the inhibition at this time of the effect of the action of other stimuli are presented in his survey by Wooldridge (1965, pages 199-202).

The role of the dominant focus is not restricted only to the "attraction" of extraneous afferent signals. The focus is a factor which changes the entire behavioral reaction of the organism.

In this conjunction, we must discuss several modern concepts of mechanisms of behavioral reaction.

The electrophysiological studies of Magoun and other investigators have shown that the activity of higher portions of the central nervous system, especially the cerebral cortex, are dependent to a considerable degree on influences that reach the cortex from the reticular formation of the brain stem (Magoun, 1965).

The afferent impulses reach the cortex, not only along the "classical" (lemniscate) pathways, but also through the reticular formation of the brain stem. The reticular formation increases the excitability of the cerebral cortex, and we can therefore assume that the dominance, i.e., the formation of optimum excitability of certain branches of the central nervous system, obviously can arise only with the participation of the influence on the cortex of impulses from the reticular formation of the brain stem.

The response reaction of the organism to each signal is preceded by an analysis of this signal, i.e., comparison with traces of past similar signals. This step obviously occupies several tenths of a millisecond and

coincides in time with the appearance of a secondary bioelectric response of the electrocorticogram (Kositskiy, 1962a, 1966b).

We know that the reactions which proceed according to the dominant procedure are produced either by a new stimulus which is unknown to the organism (orienting reflex; Vinogradova, 1961), or a signal which carries some important information for the organism.

In this case, a great many nerve elements are activated which have the ability to carry out certain directed activity in the best manner.

Consequently, before a certain state of increased excitability develops ("constellation of centers"), insuring the development of a given activity of the organism, the central nervous system performs the comparison of all afferent signals reaching it with the traces of past stimuli. If this /169
analysis shows that the previous signal does not require a change in behavior, the excitability of the "constellation of centers" (providing a transition to some new activity) will not increase. The reaction of the nervous system will remain local (economical). Then the response reaction of the organism either will not take place at all, or it will occur as an automatic act (Kositskiy, 1962a, 1965b).

However, if it happens that the signal by virtue of its nature requires the performance of a new active reaction on the part of the organism, i.e., a change in behavior, a "program" develops which prepares for such activity. The subsequent behavior of the organism is regulated by this new "program", i.e., each element of activity is directed according to the given "part of the program" and corrected by the results of "comparison" of this step of the program with the information reflecting the nature of the performance by the organism of the conditions of this stage of the program.

A very simple block diagram of the apparatus for regulating the motor activity of an organism in this case, according to N. A. Bernshteyn (1966), is shown in Figure 66.

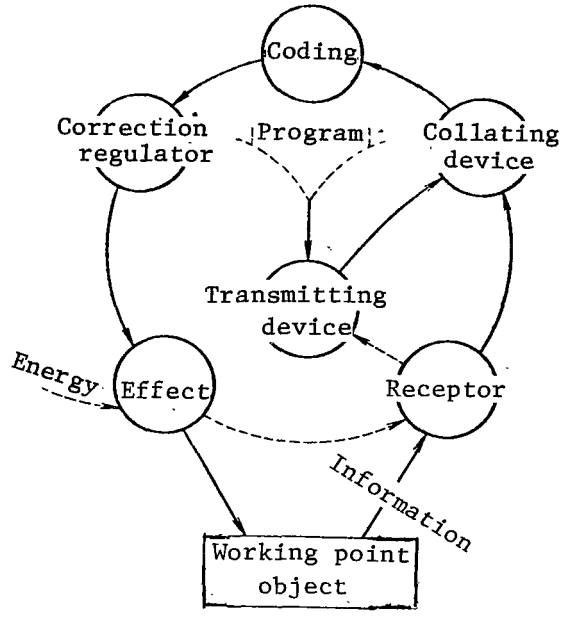

Figure 55. Simplified block diagram of control apparatus for movements (after Bernshteyn, 1966).

A. A. Ukhtomskiy stressed that each dominance ceases to exist when the afferent signals bring information that the activity for whose performance the given dominance arose has been performed. However, the signal to terminate the existence of the dominance arises, according to N. A. Bernshteyn, from the "comparison mechanism".

In this case, the system reflects the organization of the control by a certain motor act. However, the dominant may also be a "sensor". The state of dominance in man may arise in connection with signals from a second signal system. The dominance may arise in a purely psychic sphere. It may exist also as a "latent dominance", such as readiness for an action, a dominance which arises as a result of the action of signals of a certain situation. In this case, it may be triggered by any afferent signal, specific or nonspecific (i.e., capable of causing another effect under different circumstances). The latter fact has been called "switching". This phenomenon was studied by E. A. Asratyan et al (1938). Latent psychological dominance in man takes the form of a "plan" which determines further behavior, each step of which takes the form "TOTE" (Test-Operation-Test-Exit) (Miller, Galanter and Prebram, 1965).

The most complete system for any behavioral act was worked out by P. K. Anokhin in his theory of the functional system, which appeared in preliminary form in his works from 1932-1935. The most important aspects of /170 this effect, the action and reaction of an organism, are: 1) Afferent synthesis (i.e., synthesis of all information regarding the state of the

organism and the conditions of the medium, which are a necessary condition for the making of any decision); 2) The solutions adopted; 3) The efferent program of action; 4) The acceptor of the action, setting the parameters for future results; 5) The obtaining of the result; 6) The reverse afferentation regarding the parameters of the result; 7) The process of comparison of the parameters of the actually obtained result with the parameters predicted or planned in the acceptor of the action (Anokhin, 1968, 1969).

These studies have introduced considerable changes in the classical diagram of traditional behavioral reflex activity. It is necessary to have further investigations so that we can clarify the relationship between the functional system and the dominance. The dominance apparently is a functional system (or a complex of functional systems) which determines (or determine) the behavior of the organism at a given moment and actively prevents the appearance of other forms of activity, other actions and other reactions of the organism (Anokhin, 1958, page 343).

It must be emphasized that at the present time we are still at the very beginning of studies of the mechanism of dominance.

Even the latest information on this subject ("Mechanisms of Dominance", 1967) contains only an analysis of separate aspects of this phenomenon, but still does not give any idea of the structure of the dominance as a whole in the light of modern neurophysiological concepts. /171

"A shortcoming of the theory of dominance is the absence of attempts to understand the physiological nature of dominance and the mechanisms of revelation of this dominance by triggering or provocative stimulation....." states P. K. Anokhin. "Where does the excitation deviate from its own path to that of the dominant activity? What is the nature of the domination itself? What are the mechanisms of inhibition of the dominant activity of all other activities of the organism? Unfortunately, we are still not in a position to give suitable answers to many of the questions that arise in this

regard, although (as will be seen below) there are many paths for experimentation in this direction" (Mechanisms of Dominance", 1967).

At the present time it is quite clear that when a situation arises which calls for the initiation of certain activity or behavior of an organism, this in itself inhibits all other activity. These facts were linked by I. P. Pavlov to phenomena of "external inhibition", and A. A. Ukhtomskiy explained them from the standpoint of the theory of the dominant.

The formation of a similar dominance, which at a given moment inhibits all other reactions of an organism, made it possible for us to suppress reactions even to certain pathogenic stimuli and to prevent the development of certain pathological processes. Although the concept of the dominant role of the mechanisms of the dominant and the inhibition of pathological processes may only be expressed at the present time from the standpoint of a working hypothesis, it seems to us that these facts can be of definite importance for the prevention of pathological processes in man.

Dominance and Prophylaxis of Disease in Man

In 1956, the author of the theory of stress came out with a large monograph entitled, "The Stress of Life" (Selye, 1956).

"The soldier, wounded in battle; the mother, upset over her soldier son; the gambler, watching a race; the horse and jockey, on which he has bet — all of these are in a state of stress. The beggar suffering from hunger; the glutton stuffing himself, the little shopkeeper with his constant fear of bankruptcy and the rich merchant, striving for another million — all of these are in a state of stress," writes the author.

"Stress", according to Selye, is a "general sign" of all adaptive reactions of an organism. A constant state of "stress" leads to exhaustion of "adaptational energy", the supply of which is strictly limited. Disruption of adaptive reactions ("diseases of adaptation") are linked by Selye

with the development and course of various dystrophic processes, inflammatory reactions, as well as diseases of the cardiovascular system, kidneys, occurrence of eclampsia, rheumatic diseases, tuberculosis, allergic and hyperallergic ailments, nervous and psychic problems, sexual malfunctions, diseases of the digestive organs, disruption of metabolism, disruption of resistance in general and even the progress of cancer.

Naturally, the question arises of how one should live in order to avoid exhausting one's "adaptational energy" and contracting "diseases of adaptation."

Let us first evaluate the attempt to find a "common denominator" for all the very complex influences of modern life. The attempt to replace the contradictions of human life, generated primarily by social causes, by a biological concept of "stress", to replace social factors by some kind of biological equivalent, means going down the road which is characteristic of "social Darwinism", "social Freudianism" and other "-isms" that attempt to replace the social by the biological.

It is impossible to agree with such an attempt to use the concept of "stress". It is natural that these attempts have evoked the proper critical comments in our literature. Some of them appear at the beginning of this chapter. An analysis of the philosophical positions of Selye is presented in the work by G. I. Tsaregorodtsev and S. A. Chesnokova (1962). These authors write as follows: "The philosophical views of Selye are highly contradictory. If the original generalization of experimental data has a spontaneous-materialistic, and sometimes mechanistic nature (failure to consider the role of higher nervous activity, absolutization of the pituitary-adrenal system, metaphysical concepts of the relationship of general and specific reactions, etc.), his general biological and philosophical outlooks are idealistic. It is necessary to mention in this regard that Selye does not share the principles of any single idealistic trend, but eclectically combines the fundamental positions of many philosophical and medico-biological

idealistic trends and concepts, such as Freudianism, psychosomatics, physiological idealism, vitalism, etc."

It is not our concern to present a detailed analysis and criticism of the philosophical aspect of Selye's concepts and views. The present work is devoted to biological and medical aspects of the problem of "stress".

One of the characteristic signs of our time (with its increasing speeds of machines and productive processes, with the revolutionary strides made by science and the rapidly swelling tide of information) is an increasing stress in the tempo of life.

The state of stress is made more severe by social collisions in class society, torn by internal contradictions, and the greed of imperialism. Emotional stress is increased by the threat of a new war, the suppression of basic human rights in many countries, hunger and disease in our world, split into antagonistic camps. Selye's well-chosen term "stress" became a sort of general sign of the influence of conditions of modern life on man. /173

"Nervous stress", "psychic stress", "emotional stress", just "stress", which are similar to "exhaustion", "aging", "degradation", in Selye's opinion became guilty for all of our troubles, ills and sicknesses. After that, many people began to live in fear of a possible "sapping of their adaptational energy" — this new "life force" of the second half of the Twentieth Century. But if we adopt this apt term, do we have to agree with its content or initial treatment? No absolutely not!

Don't we use the expression "atom" ("indivisible") in an age when atomic fission has created a new era in the development of science and industry? Don't we use the expression "guinea pig", knowing full well that it is neither a pig nor has anything to do with Guinea?

The same is true of the term "stress". By using this apt expression, we are not at all obliged to make any contributions to the meaning which its author gave to it originally.

What thinking person does not feel like protesting against the idea that all our poor could be helped by an injection which contained hormones necessary for the organism (in a stage of "exhaustion of adaptive energy")? Could our philosophy, reflecting life and all the depths of its contradictions, agree with such an approach? And does not the scarcity of ways suggested to man from escaping the state of "stress" characterize the concept itself? The term "stress" means "pressure". But for man this is primarily nervous pressure, it is a change of the manner of behavior and thought; it is the development of new dominances.

So, let us answer first of all the question: should we be afraid of "pressures" at all, and is it valuable in any way to protect oneself against "stress", in order to prevent disease?

We must emphasize that Selye was not the first to say that in the course of life there is only expenditure, loss of "adaptational energy", the supply of which is strictly limited. His views in this regard are close to those of scientists who feel that the cause of aging is the consumption of "certain substances" (Zhak Leb); "the life enzyme" (Byuchli); "special energy" (Rubner). Indeed, even Gerbst, Kortel't and others felt that the organism "breaks down like any machine" as it ages. But if we accept the /174
view that during one's lifetime there is only the consumption of certain substances or energy without corresponding replacement of them, we must assume that "the supply of these substances or factors was given to all mankind by 'Great-Grandmother Eve'."

Similar "theories" lead to the "conclusion" that weakened processes of vital activity promote longer life. In reality, the opposite is the case: intense metabolism in an organism is often accompanied by a significant

length of life, and, as observations show, people who have reached great age have often led active lives, engaged in steady hard work.

Even F. Engels, emphasizing the dialectic nature of biological phenomena, mentioned that the processes of exhaustion and breakdown of structures in a living body are a necessary prerequisite for their replacement. We know that the replacement and creation of structures in the living body is possible only during the process of their activity without which degeneration sets in, together with degeneration and death of all cells, organs and tissues.

The facts which indicate this were obtained in many studies of biological phenomena conducted at all levels — molecular, cellular, organic and on the level of the intact organism. Even the doctors of antiquity were well acquainted with the important role of an active life for maintaining health. In our day, the student of I. P. Pavlov, G. V. Fol'bort, studying processes of regeneration of functions of the salivary glands following their exhaustion, declared that the processes of recovery took place more intensely when the exhaustion of the glands was more pronounced.

The positions of Engels have been supported recently by the achievements of molecular biology and cytophysiology. Hyperfunctions of the cell, intensifying its activity, lead to an increase in the amount of nucleic acids (DNA and RNA) promoting the synthesis of specific proteins that participate in the accomplishment of a given function.

In recent years, a large amount of experimental data has been obtained which indicates that an increase in the function of any cell leads to the activation of a genetic apparatus, as a result of which there is an acceleration of the synthesis of specific proteins that promote the accomplishment of that function. These facts are explained on the basis of the hypothesis of Jacob and Monod, 1961.

These facts were obtained in studies of processes of regeneration of the liver, kidneys and other internal organs, hypertrophy of the heart, hyperfunction of the nerve cells, etc.

Exhaustive surveys of the literature on this question were presented in the symposium "Regulatory Mechanisms of the Cell" (1964), and in the works of L. D. Liozner (1963), F. Z. Meyerson, 1965-1967), V. Y. A. Brodskiy (1966), V. V. Dergachev (1967), Ye. N. Sokolov (1969), et al. It is very important at the present time that such data have been obtained in studies of the re- /175
lationship between the function and genetic apparatus of nerve cells. Increased activity of nerve cells produces an increase in the mass of their functional proteins, a thickening of the axons, etc. This is accompanied initially by a decrease and later by an increase in the amount of RNA in the Nissl substance and an increase in the synthesis of RNA in the nucleolus of the cellular nucleus (Hyden, 1960, 1964, 1965; Morrel, 1966; Brodskiy, 1966; Meyerson, 1967).

Similar data were obtained in connection with the heart. Hyperfunction and hypertrophy of the heart increased the amount of RNA in the myocardium. It was observed in this connection that the increase in the amount of DNA is proportional to the increase in the mass of the heart, which occurs in hypertrophy. Thus, the activity of the differentiated cells under conditions of an intact organism takes place on the basis of interaction between three basic processes: physiological function, energy formation, and protein synthesis (Meyerson, 1966).

A certain rate of functioning of structures of differentiated cells corresponds to a certain intensity of breakdown of these structures. The macromolecular products of decay of cell proteins that are created as the result of breakdown — "metabolites of breakdown" — may be cast in the role of factors which act through the mechanism described by Jacob and Monad (1961) for regulation of protein synthesis, activating the synthesis of RNA in the structural cystrons of chromosomal DNA. As a result, there is activation of protein synthesis and nucleic acids.

An important aspect of the activation of the genetic apparatus is obviously the increase in DNA-dependent synthesis of RNA, and the increased formation of RNA in turn is a prerequisite for the activation of protein synthesis (Meyerson, 1967).

We shall emphasize here the role of activity for retention of the structure and function of any cell, organ and tissue. This position also refers to the organism as a whole.

For man, this activity is primarily labor. Academician A. A. Bogomolets correctly emphasized that the whole organism must work: all of its organs, so that not one function is forgotten. For the problems which are handled in this book, it is important that the role of activity and labor in man not be applied only to insuring the processes of synthesis of proteins and maintaining tissue structure. One must not forget the moral factors of human life which labor affects. We know how important a role is played by any labor or work which brings joy and the feeling of satisfaction. An especially im- /176
portant role is assigned to inspired labor, the joy of creation itself. We know that in this case a state of dominance arises, and that this state is accompanied by increased resistance of the organism, increasing its stability against the action of a number of unfavorable factors. It would be superfluous here to give the many examples that come to mind, indicating that the enthusiasm generated by high goals which a man sets himself helps him to overcome any obstacles, elevates, not only the morale, but also the physical resources of the organism, increasing also the resistance of the organism to the action of many pathogenic stimuli. At the present time, we still have not defined the mechanisms of these very important phenomena for human health. It is indisputable, however, that the principle of dominance plays a part in many of them.

I. P. Pavlov emphasized that a very important thing in successfully overcoming the difficulties of life is the type of nervous system. The same effects, the same hardships can cause breakdown, collapse, illness in

one organism, while in another nothing happens. A strong nervous system can handle difficulties which would be fatal for a weak nervous system.

In the Pavlovian laboratories it was shown that under the influence of certain living conditions, specific types of nervous activity regularly develop. A greenhouse or hothouse type of upbringing, protection against the hardships and difficulties of life, unavoidably leads to the development of a weak type of nervous system, which can collapse into breakdown and neurosis under slight stress.

A strict upbringing, gradual acclimatization to overcoming difficulties, etc., leads to the development of a strong nervous system.

It is possible, as I. P. Pavlov said, to carefully "develop the nervous system infinitely".

The entire life of a human being, beginning with the cradle, further upbringing, the entire conscious activity, is a continuous "training" which can lead to the development of striking stability of the nervous system.

However, in the case when the directed activity leads to exhaustion and requires regeneration of strength, is not an active vacation a good rest for a healthy man, i.e., switching to new interests and new activity?

And is it not a well-known fact that the more interesting these new occupations are and the more intensive this new activity, the more valuable the vacation, the more complete the regeneration of the ability to work? Don't we know that in order to tear a man away from the endless circle of daily occupations, to relieve him of the burden of his cares, it is necessary to give him first of all a spiritual "breathing space", filled with interesting new activity? Isn't it so that "like cures like" and that "only a woman can save a woman", that it is necessary not to wrap one's self up in sorrow, not to give way to one's sadness, but to try to find some diversion? Isn't the best way to do this to take a trip, to go on a tour, to change one's

apartment, one's living conditions, etc.? Isn't the best way for a man to get a rest from his usual labor, to do intensive physical labor?

In all these cases, we are not saying that we want to get away from /177
"stress"; on the contrary, we are saying that it is better to create a new kind of "stress" which will relieve the old. But let's stop playing with words. What we are dealing with here, of course, is a creation of a new dominance which extinguishes, suppresses, inhibits the old one.

Inhibition of pathological processes from this standpoint is only a partial case, only only one of the phenomena of the basic property of dominance: its ability to extinguish all other activity and any other reaction to the organism.

We will not be so bold as to make any practical recommendations in this book which would be required for training the nervous system for a rational mode of life, work and rest. We have touched here only on the theoretical aspects of the problem. Obviously, it is not cowardly to avoid situations which create the state of "stress", but inspired boldness in overcoming difficulties must become our motto, rather than fear of any possibility of "exhaustion of adaptational energy", and the creation of conditions such that the protective forces of the organism, regulated by the nervous system (and the nervous system itself) will be strengthened and reinforced through practice.

Our organism is not the pantry of a miserly knight — the resources of "adaptational energy" in it cannot be put back as they are used up. Only sensible activity, harmonically included in the function (i.e., intensive function) of all systems can serve as a reliable means of combating degeneration and exhaustion. Is it necessary to repeat that intensive activity can be assured only with the appearance of strong dominances, whose origin lies in the sphere of higher human interests? And the fact that the development of each of these dominances must simultaneously suppress the receptivity of the organism to the action of many harmful agents, — is this

not an encouraging answer to the question of how to structure our lives? To be afraid of difficulties, or to oppose them and learn to overcome them; always afraid of stress, or understanding that reasonable stress is unavoidable, and that without it there can be no development of the strength of the nervous system and the strength of the personality; this is our moral stimulus, the basis of our progress.

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